(+)-DESOXOPROSOPININE: A MODEL FOR THE TOTAL ASYMMETRIC SYNTHESIS OF *PROSOPIS* ALKALOIDS

by

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A thesis submitted to the Graduate Faculty of
North Carolina State University
in partial fulfillment of the
requirements for the degree of
Master of Science

DEPARTMENT OF CHEMISTRY

Raleigh, North Carolina

1999

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REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	27.Jul.99	THESIS

4. TITLE AND SUBTITLE
(+)-DESOXOPROSOPININE: A MODEL FOR THE TOTAL ASYMMETRIC SYNTHESIS OF PROSOIS ALKALOIDS

5. FUNDING NUMBERS

6. AUTHOR(S)
1ST LT SANDELIER MATTHEW J

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
NORTH CAROLINA STATE UNIVERSITY

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
THE DEPARTMENT OF THE AIR FORCE
AFIT/CIA, BLDG 125
2950 P STREET
WPAFB OH 45433

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
FY99-196

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Unlimited distribution
In Accordance With AFI 35-205/AFIT Sup 1

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS	15. NUMBER OF PAGES	16. PRICE CODE
	86	

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

Abstract

SANDELIER, MATTHEW J.: (+)-Desoxoprosopinine: A Model for the Total Asymmetric Synthesis of *Prosopis* Alkaloids. (Under the direction of Dr. Daniel L. Comins.)

This work develops a general synthesis of the *Prosopis africana* alkaloids, using a chiral auxiliary-mediated process. Enantiopure *N*-acyldihydropyridones were produced and used as intermediates, targeting (+)-desoxoprosopinine as a synthetic model for those alkaloids. The orientation of all three stereocenters was highly controlled, with the synthesis of intermediate **75**, just short of the target, in 7 steps with a 13.8% overall yield.

Biography

The author was born in Woodbury, NJ on March 30, 1971 to James and Margaret Ann Sandelier. In 1989, he graduated from Cherokee High School in Marlton, NJ. After attending Boston University for two years on an Air Force ROTC scholarship, Matt transferred to the United States Air Force Academy, Colorado Springs, CO. With the encouragement of the faculty, including a Comins' group graduate, Dr. Michael Killpack, the author began his studies in organic chemistry.

After graduation, Lt Sandelier was assigned to the High Explosives Research and Development (HERD) Facility at Eglin AFB, Fort Walton Beach, FL. For two years he worked as a research chemist formulating and testing new explosives for USAF developmental munitions. Then in August 1997, he was given the opportunity to pursue his Master's Degree at North Carolina State University, Raleigh, NC, sponsored by the Air Force Institute of Technology.

Acknowledgements

I would like to thank Dr. Daniel L. Comins for his invaluable direction and encouragement throughout this project. I must also recognize the other members of the Comins' group, for both their academic and personal support. I am deeply indebted to the members of my committee, Dr. Suzanne Purrington, and Dr. Samuel Levine, for their diligence in the editing of this manuscript. Lastly, I must thank the Air Force Institute of Technology and North Carolina State University, for the wonderful educational opportunity that I have been given for the past two years.

Table of Contents

List of Schemes

Page

List of Figures

Page

List of Tables

Page

List of Abbreviations and Terms

Abbreviation or Term	Explanation
$[\alpha]_D$	optical rotation
Anal.	analysis
aq	aqueous
bp	boiling point
br	broad
brine	saturated aqueous sodium chloride
Bu	butyl
n-BuLi	*n*-butyllithium
t-BuLi	*tert*-butyllithium
°C	degree(s) Celsius
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
calcd.	calculated
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
cm^{-1}	reciprocal centimeters
δ	chemical shift in ppm from tetramethylsilane
d	doublet
dd	doublet of doublets
de	diastereomeric excess
dm	decimeter
DMF	*N,N*-dimethyl formamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
eq.	equivalent(s)
Et	ethyl
Et_2O	diethyl ether

EtOAc	ethyl acetate
EtOH	ethanol
g	gram(s)
GC	gas chromatography
h	hour(s)
H^+	proton or protic acid
^1H NMR	proton nuclear magnetic resonance spectroscopy
HOAc	glacial acetic acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IR	infrared spectroscopy
J	coupling constant
Kcal	kilocalorie(s)
LDA	lithium diisopropylamide
lit.	literature
M	molar
m	multiplet
Me	methyl
MeOH	methanol
mg	milligram(s)
Mhz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
N	normal

NaHMDS	sodium bis(trimethylsilyl)amide
NIH	National Institutes of Health
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
radial PLC	radial preparative-layer chromatography
rt	room temperature
s	singlet
t	triplet
TBAF	tetra-*n*-butyl ammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butylchlorodiphenylsilane
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
t-Bu	*tert*-butyl
TCC	*trans*-2-(α-cumyl)cyclohexyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

Introduction

Chiral *N*-Acyl-2,3-dihydro-4-pyridones:

Chiral *N*-acyl-2,3-dihydro-4-pyridones have been used extensively as intermediates in the asymmetric synthesis of various indolizidine[1], quinolizidine[2], and piperidine[3] alkaloids (Figure 1). The versatility of these intermediates stems from the ability to substitute stereoselectively at each of 2,3,4,5, & 6 carbons of the dihydropyridone skeleton.

Chiral *N*-acylpyridinium salts are the backbone of the current Comins' group chemistry, and are the basis for synthesizing enantiopure 2-substituted 2,3-dihydro-4-pyridones[4]. By adding a chiral chloroformate to 4-methoxy-3-triisopropylsilyl-pyridine **1**, a pyridinium salt **2** is formed which is susceptible to a facially selective attack by an organometallic nucleophile at the C-2 position (Scheme 1). Subsequent acid hydrolysis of the dihydropyridine **3** *in situ* produces a diastereomeric mixture of enantiopure 2-substituted 2,3-dihydro-4-pyridones **4**.

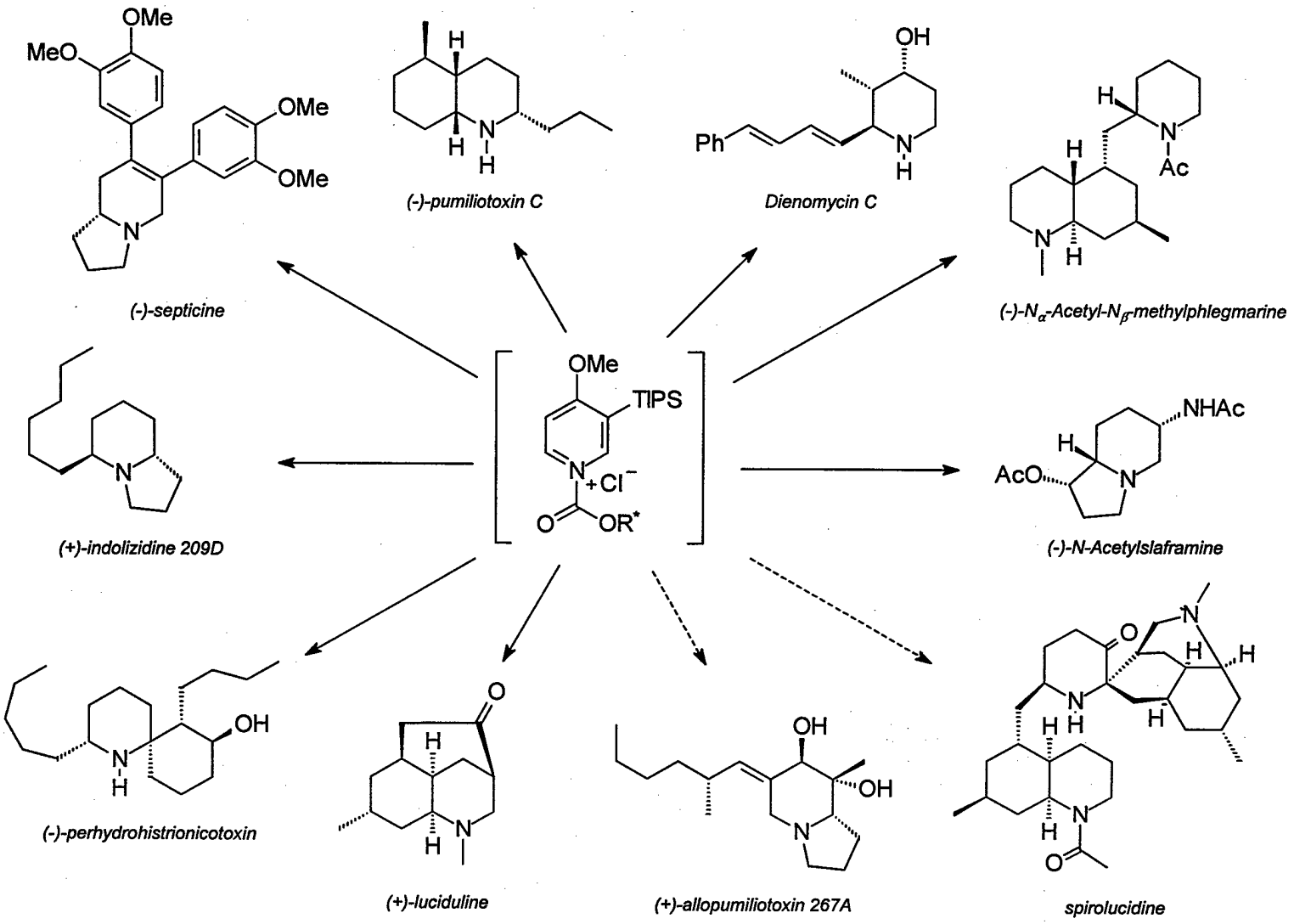
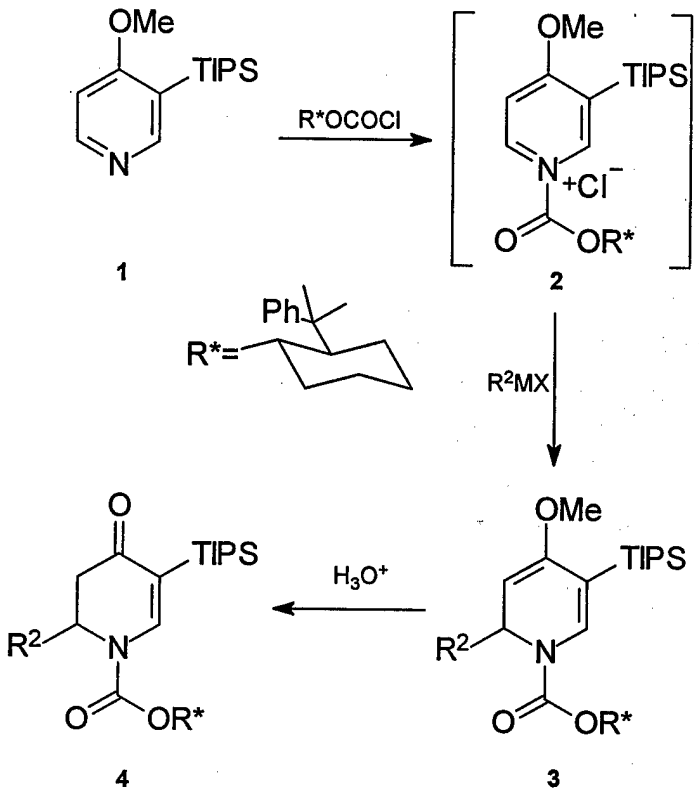


Figure 1: Past and Future Targets using Chiral *N*-Acyl-2,3-dihydro-4-pyridones

Scheme 1: Synthesis of Chiral *N*-Acyl-2,3-dihydro-4-pyridones



This facial selectivity is controlled by the use of two modifications to a basic pyridinium salt. The first is a chiral auxillary, *trans*-2-(α-cumyl)cyclohexanol (TCC), whose enantiomers are isolated by kinetic resolution[5]. The structure of this auxillary, when incorporated into the *N*-acylpyridinium salt, is specifically designed to overlap one face of the pyridine ring. The second facial director is the 3-triisopropylsilyl group. This bulky group not only blocks the 2-position of the pyridine ring from attack from either side, but also plays a role in the alignment of the chiral auxillary, increasing the facial selectivity of the attacking nucleophile. Rotation about the carbon-nitrogen

bond of a pyridinium salt is normally not restricted. However, the combination of steric interactions between the chiral auxiliary and 3-silyl group and possible π-π interactions between the phenyl ring of TCC and the pyridinium ring contribute to the limited rotation about that bond. Figures 2 & 3 show molecular mechanics (MMX) representations of the two most stable rotamers. The population of rotamer A is significantly higher than rotamer B, and thus high diastereoselectivities are obtained.

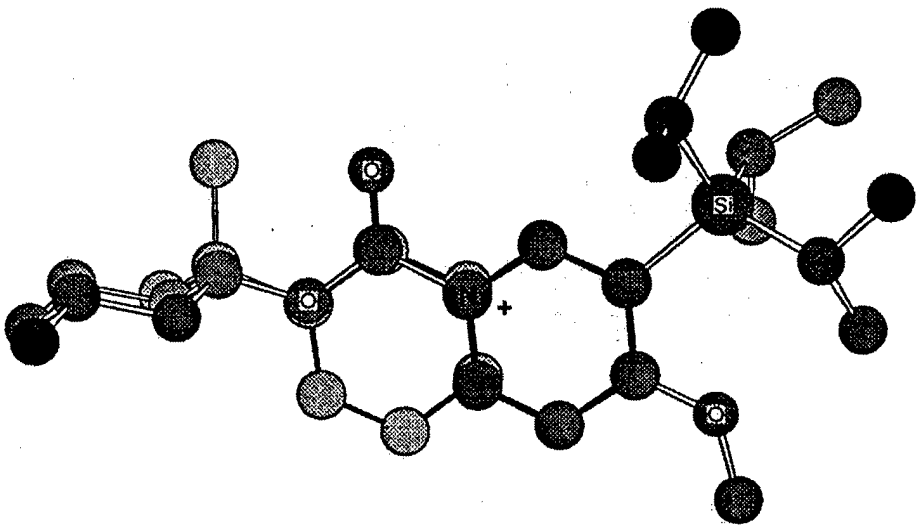


Figure 2: Rotamer A

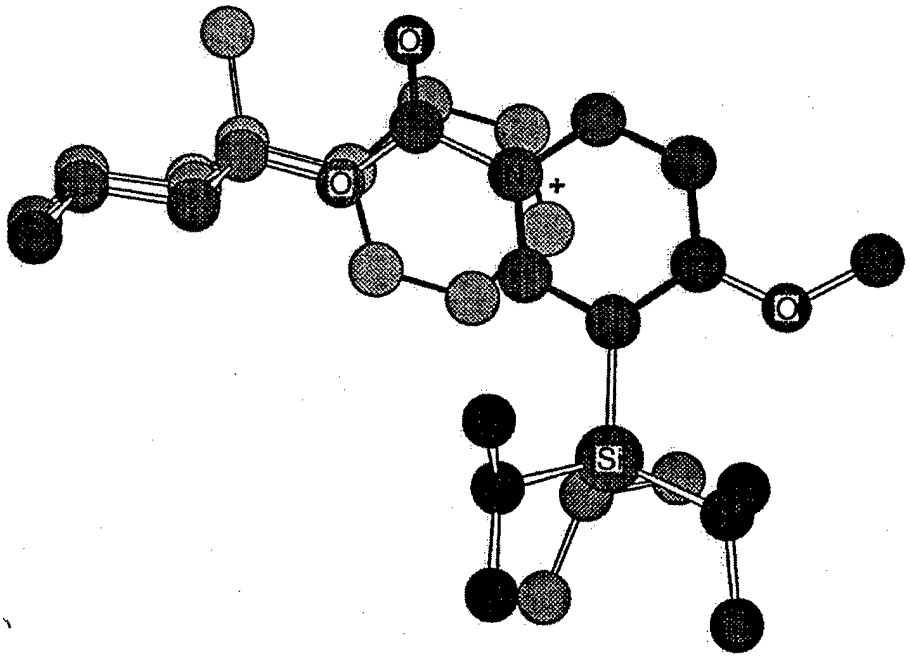


Figure 3: Rotamer B

Once this enantiopure 2-substituted dihydropyridone is formed, substitution at the other carbons can be achieved through a number of methods. Through enolate formation, producing an N-acyl stabilized dihydropyridine, the C-3 position can be alkylated[1c,3d,6]. Either 1,2- and 1,4 additions or reductions can be used to substitute C-4 and C-6[1b,7]. Finally, the C-5 position can be electrophilically substituted[7].

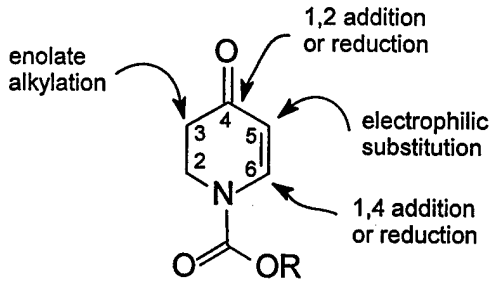


Figure 4: Substitution of *N*-Acyl-2,3-dihydro-4-pyridones

The stereoselectivity of all of these substitution methods relies on the conformation of the dihydropyridone. Steric interactions between the N-acyl group and the new C-2 substituent, $A^{(1,3)}$ strain, cause the dihydropyridone to be somewhat rigid, with the C-2 substituent remaining axial (Figure 5)[8]. This conformational bias effects considerable control over the stereochemistry at all the positions of the dihydropyridone.

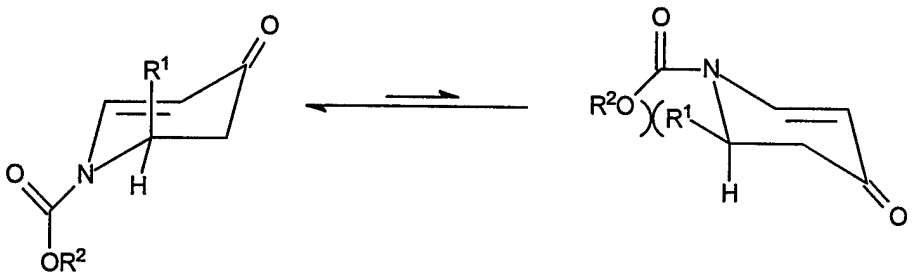


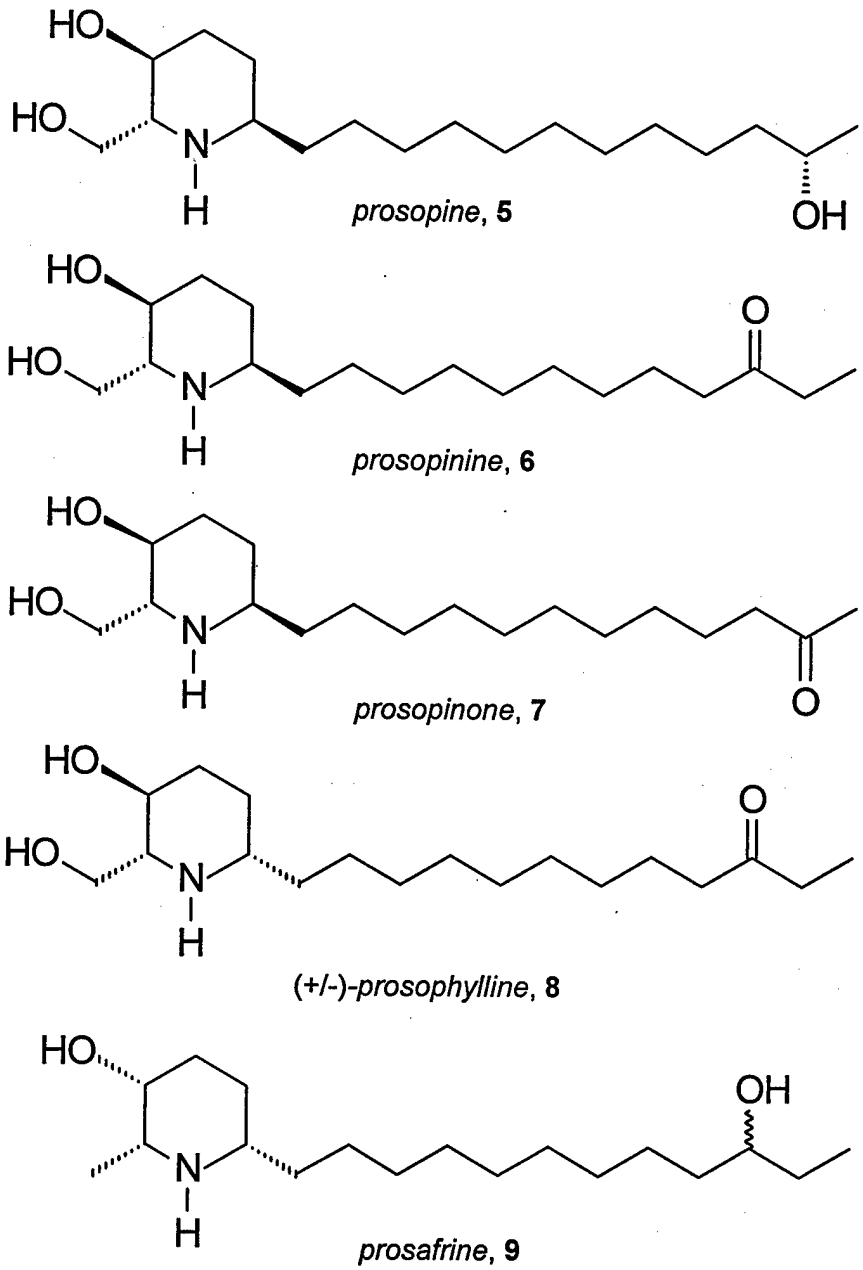
Figure 5: $A^{(1,3)}$ strain in *N*-Acyl-2,3-dihydro-4-pyridones

Isolation and Structure Determination of *Prosopis africana* Alkaloids:

Several 2,6-disubstituted piperidin-3-ol alkaloids have been isolated from the *Prosopis africana*[10], whose leaves have been used in Africa to treat toothaches[9a]. These alkaloids **5-9**, shown in Figure 6, all have a hydroxyl group in the 3-position, an *n*-C_{12} side chain in the 6-position, and either a methyl or hydroxymethyl group in the 2-position.

The structure of these alkaloids was determined by a series of reactions degrading the molecules to known compounds and using mass spectrometry for identification. First, by an Oppenauer oxidation, *prosopine* **5** could be transformed into *prosopinone* **7**, which was shown to be isomeric with *prosopinine* **6**. Then, by Wolff-Kishner reduction, both *prosopinine* **6** and *prosopinone* **7** were transformed into the same compound, desoxoprosopinine, proving that all three had the same stereochemistry about the piperidine ring, and differed only in the substitution of the C-

6 side chain. The same sequence, when applied to *prosophylline* **8**, produced a different compound, proving its piperidine ring stereochemistry was different[9,10].



prosopine, **5**

prosopinine, **6**

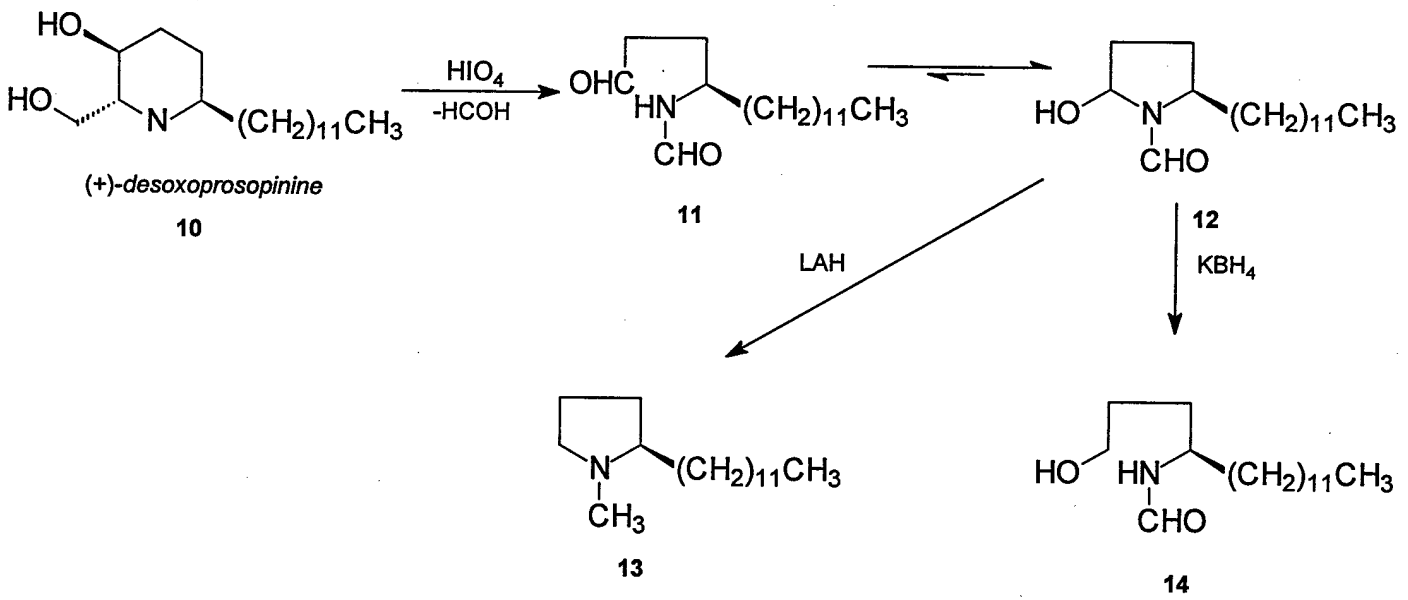
prosopinone, **7**

(+/-)-*prosophylline*, **8**

prosafrine, **9**

Figure 6: *Prosopis africana* Alkaloids

Scheme 2 : Periodate Oxidation of Desoxoprosopinine



(+)-*desoxoprosopinine*

10

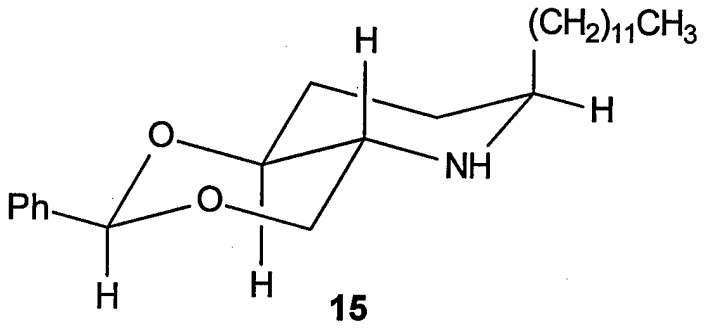
11

12

13

14

Next, a periodate oxidation of desoxoprosopinine resulted in a tautomeric mixture of **11** and **12**, favoring prosopinamide **12**. This mixture was subjected to both LAH and KBH_4 reductions giving products **13** and **14,** respectively (Scheme 2)[9,10]. The relative stereochemistry of the piperidine ring was established by forming the *O,O'*-benzylidine derivative **15** by reacting desoxoprosopinine **10** with benzaldehyde (Figure 7). NMR coupling constants were used to determine the *trans* relationship between both C-2 and C-3, and C-2 and C-6[9b,10].



15

Figure 7 : *O,O'*-Benzylidene Derivative of (+)-Desoxoprosopinine

Horeau's method of kinetic resolution[11] was used to determine the absolute stereochemical configuration of *prosopine* **5** and *prosopinine* **6**. Using the C-3 hydroxyl position of *prosopinine* **6**, the configuration of all three centers on the piperidine ring were established to be (2*R*,3*S*,6*R*). For the 11'-hydroxyl group of *prosopine's* C-6 side chain, the *O,O'*-benzylidene derivative was made, and this compound was subjected to Horeau's kinetic resolution. The center was established as 11'*S*[10,11].

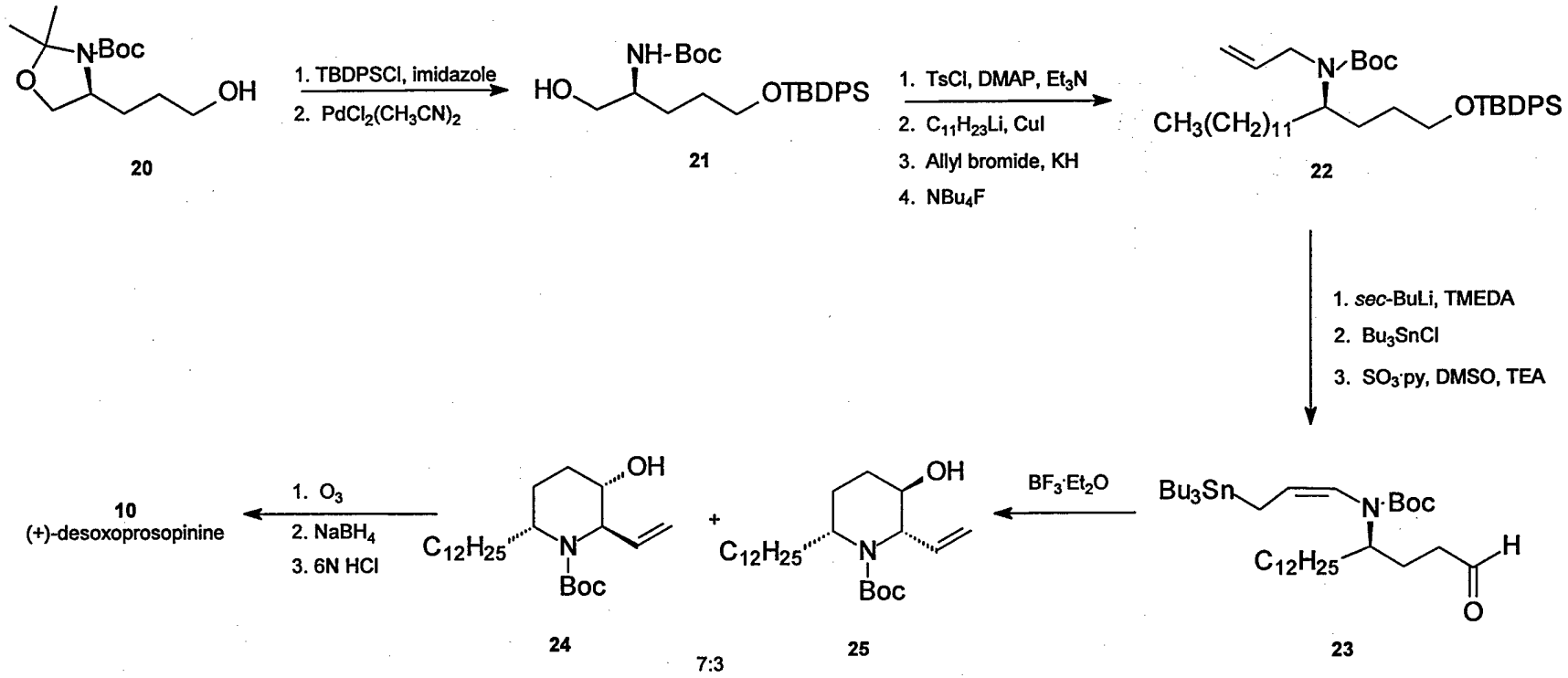
Literature Review

(+)- & (-)-Desoxoprosopinine:

The synthesis of desoxoprosopinine has been achieved by several groups[12,13] in an effort to demonstrate their ability to stereoselectively design the piperidine ring structure of the *Prosopis* alkaloids. Desoxoprosopinine has three stereocenters that need to be set in any such synthesis—C-2, C-3 and C-6. In the two cases reviewed here, the syntheses take starting materials from the chiral pool. With the orientation of either C-2 or C-3 already set, only two other centers needed to be introduced.

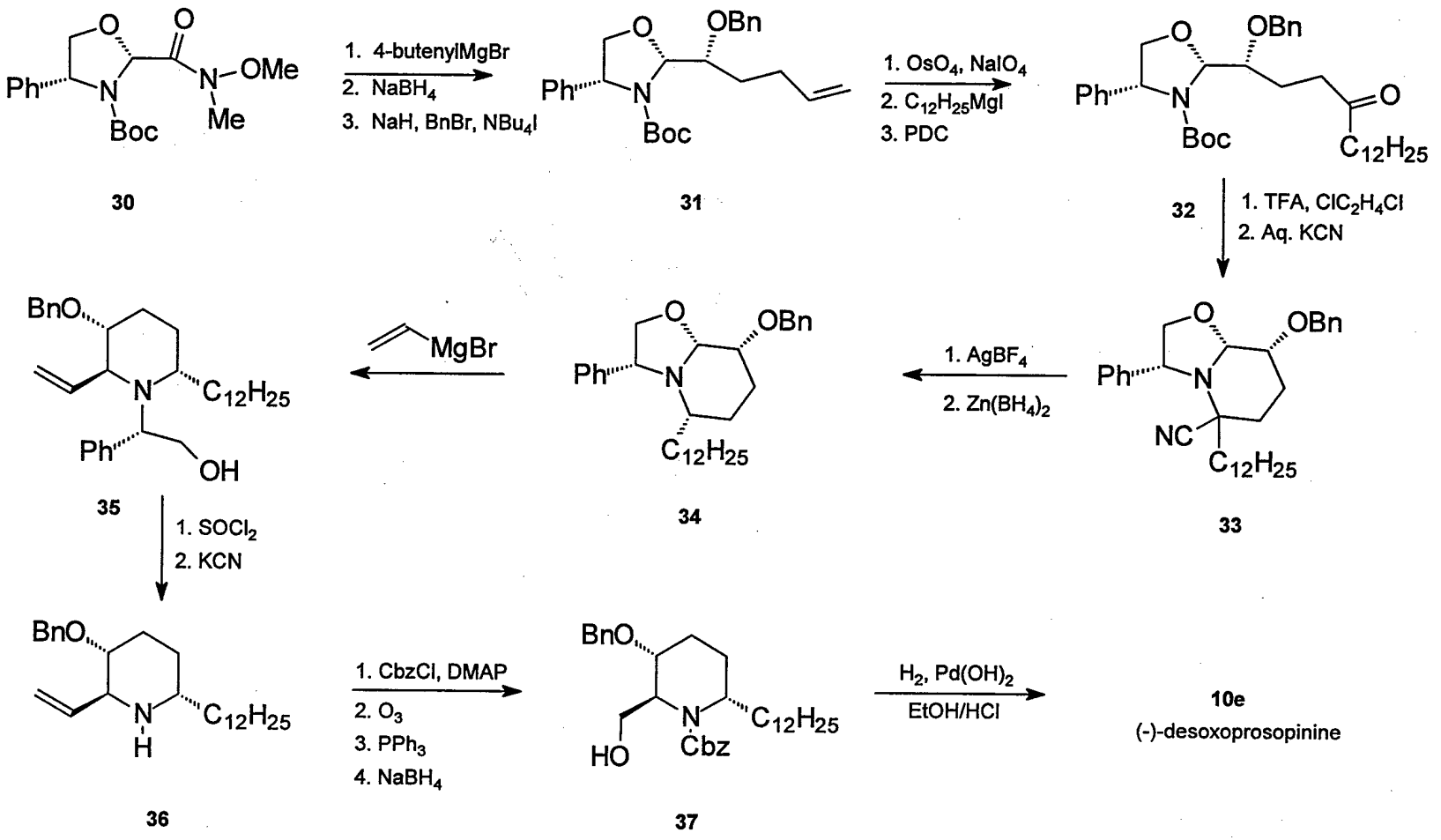
Yamamoto, et.al.[12] started with an L-glutamic acid derived starting material, **20** (Scheme 3). Silyl ether protection of the primary alcohol, followed by selective deprotection of the amine, gave compound **21**. Tosylation of the resulting primary alcohol followed by alkylation produced the *n*-C_{12} side chain of desoxoprosopinine. Next, allylation of the amine and desilylation of the primary hydroxyl group gave compound **22**. Treatment with base produced an allylic anion which was quenched with Bu_3SnCl to produce the allylstannane necessary for the key step in this synthesis—an intramolecular γ-aminoallylstannane cyclization. Cyclization induced by $BF_3{\cdot}Et_2O$ was high yielding but only moderately selective, producing a 7:3 mixture of diastereomers at C-2 and C-3. Ozonolysis, reduction, and deprotection provided (+)-desoxoprosopinine in 12 steps with a 16% overall yield.

Scheme 3: Synthesis of (+)-Desoxoprosopinine by Yamamoto, et.al.



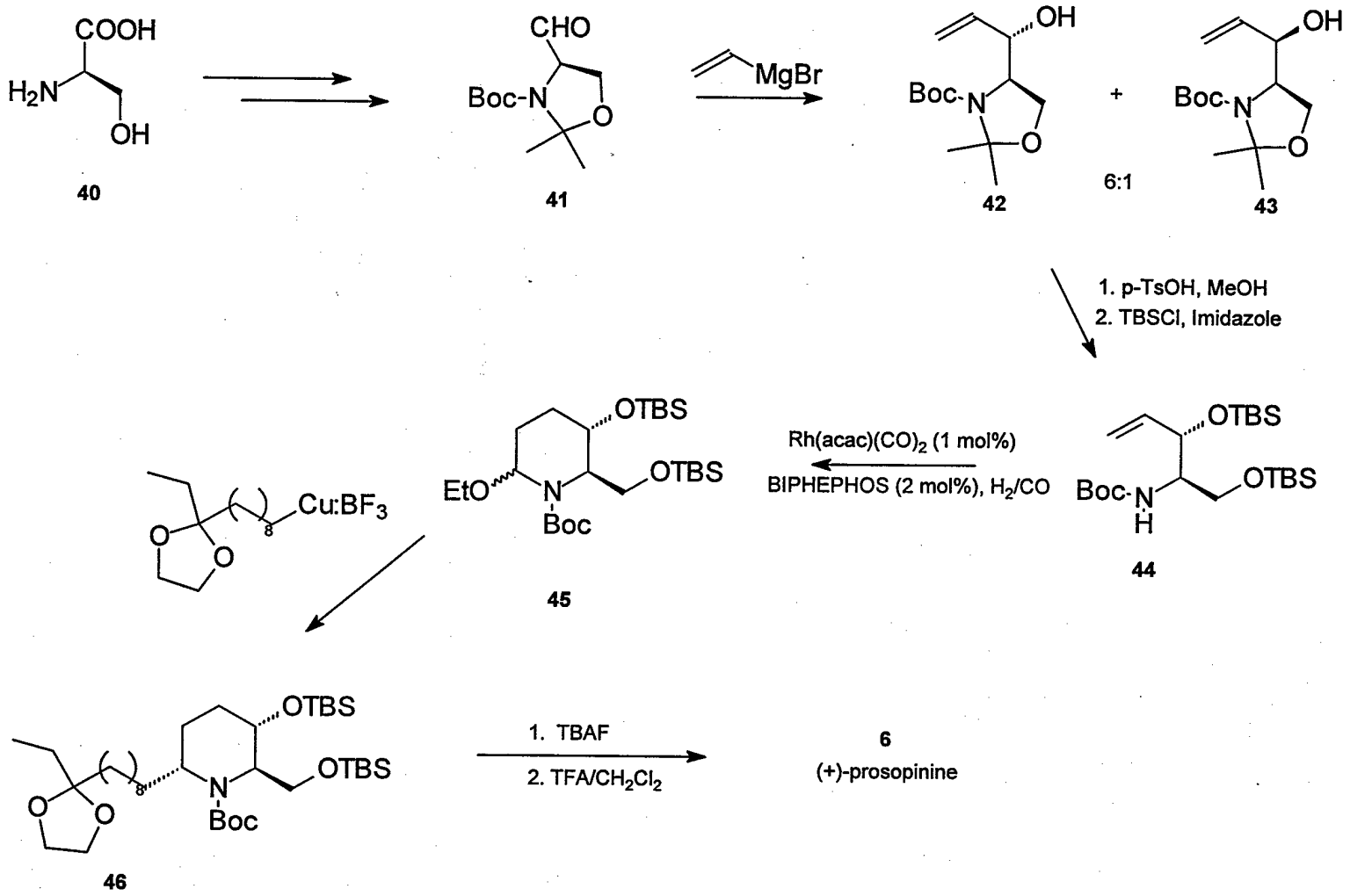
Another synthesis was done by Couty, et.al.[13] to produce the unnatural enantiomer, (-)-desoxoprosopinine **10e**. This sequence (Scheme 4) started from a Weinreb's amide **30**, which was derived from (*R*)-phenylglycinol in four steps (78% overall yield)[14]. Treatment of **30** with 4-butenylmagnesium bromide, diastereoselective reduction with $NaBH_4$, and protection of the new hydroxyl as a benzyl ether produced compound **31.** This sequence established the stereochemistry of the C-3 hydroxyl group of (-)-desoxoprosopinine. The terminal olefin of **31** was oxidatively cleaved to an aldehyde, treated with dodecylmagnesium bromide, and finally reoxidized to form ketone **32**. Acidic deprotection of the amine, followed by intramolecular condensation with the tethered ketone, formed an iminium ion which when treated with aqueous KCN produced aminonitrile **33**. This aminonitrile was diastereoselectively reduced *via* a literature method[15] to form compound **34**, setting the C-6 stereocenter of the target **10e**. Although no reagent is listed, the authors describe a Lewis-acid mediated opening of the oxazolidine ring. This formed an intermediate iminium ion, which was treated with vinylmagnesium bromide to form piperidine **35**, and set the final C-2 stereocenter. This facial selectivity is purportedly due to both the dodecyl and benzyloxy groups blocking the opposite face. The last novel step was the dealkylation of the amine. Treatment with thionyl chloride formed the primary chloride, which when substituted with cyanide, induced a spontaneous β-elimination to produce the free amine **36**. *N*-Acylation, oxidative cleavage of the olefin, aldehyde reduction, and hydrogenolysis delivered the target in 11 steps with a 12.8% overall yield.

Scheme 4: Synthesis of (-)-Desoxoprosopinine by Couty, et.al.



One successful synthesis of a side-chain functionalized *Prosopis* alkaloid, (+)-*prosopinine* (**6**), was accomplished by Ojima & Vidal[16]. This work started with the synthesis of Garner's aldehyde[17] **41** from (*R*)-serine **40**. This chiral starting material establishes the C-2 stereochemistry of the target **6**. Setting the C-3 center was accomplished with a 6:1 selectivity by treating **41** with vinylmagnesium bromide. After removal of the acetonide with *p*-toluenesulfonic acid and protection of both hydroxyl groups as the *tert*-butyldimethylsilyl ethers, intermediate **44** was ready for the key reaction. Cyclohydrocarbonylation was achieved in high yield (92%) when catalyzed by a rhodium-BIPHEPHOS complex. Generation of the acyliminium ion of **45** *in situ* and attack by the alkylcuprate of 1-bromo-10-oxo-dodecane ketal produced the fully protected (+)-*prosopinine* **46** with the proper *trans*-2,6 stereochemistry. After deprotection, the total synthesis of (+)-*prosopinine* **6** was achieved in 10 steps from **41** with an overall yield of 11.3%.

Scheme 5: Synthesis of (+)-Prosopinine by Ojima & Vidal

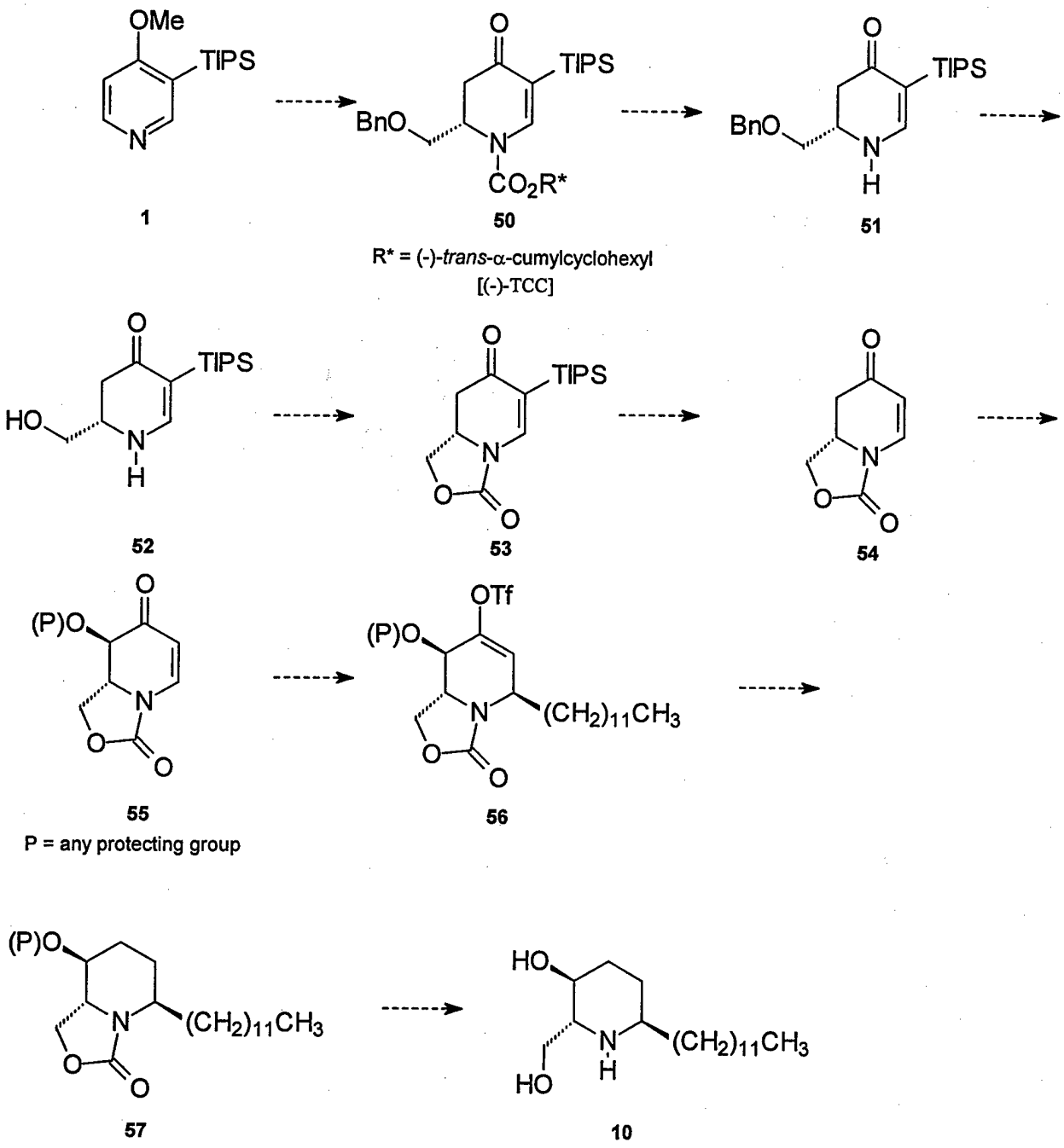


Results and Discussion

The synthetic utility of chiral *N*-acyl-2,3-dihydro-4-pyridones has been well-established in the past in the total asymmetric syntheses of various indolizidine[1], quinolizidine[2], and piperidine[3] alkaloids. This study once again demonstrates that utility in the asymmetric synthesis of (+)-desoxoprosopinine **10**. The convergence of this synthesis will also prove to be a model for the synthesis of all *Prosopis africana* alkaloids.

The original synthetic plan (Scheme 6) involved using an α-hetero-Grignard reagent as the nucleophile in the synthesis of a (2*S*)-benzyloxymethyl substituted chiral *N*-acyl-2,3-dihydro-4-pyridone **50**. After removal of the chiral auxiliary, cleavage of the benzyl ether by hydrogenolysis would produce β-aminoalcohol **52**. Cyclization of **52** would form the oxazolidinone ring in bicyclic compound **53**, which is critical in controlling the stereochemistry at C-6. This bicyclic ring system would force the 2-substituent into a pseudoequatorial orientation, and thus direct the subsequent 1,4-addition *via* a stereoelectronically-controlled axial attack[18] to produce the desired *trans* 2,6-product. However, before this 1,4-addition could be accomplished, the C-3 hydroxyl functionality must be installed *trans* to the C-2 substituent. This transformation would eventually become the most difficult step in this scheme.

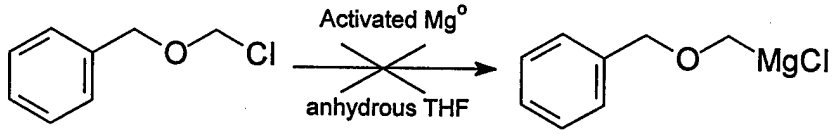
Scheme 6: Original Synthetic Plan



Formation of an α-Hetero-Organometallic Reagent

The formation of compound **50** involved the preparation of an organometallic reagent from benzyl chloromethyl ether. This chloride had been the subject of previous work[19], where the formation and stability of Grignard reagents from various chloromethyl ethers was studied. That report states that Grignard reagents of this type are extremely temperature-sensitive, both in formation and stability. However, the work also mentions that the chloromethyl allyl and benzyl ethers are somewhat more stable than the alkyl ethers, and therefore the formation of this Grignard reagent seemed a good starting point.

Scheme 7: Grignard Reagent Formation



59 **60**

Many attempts were made to synthesize Grignard reagent **60**, the conditions of which are listed in Table 1. Extensive efforts were made regarding the purity and dryness of the reagents; however, no indication of any Grignard reagent was found.

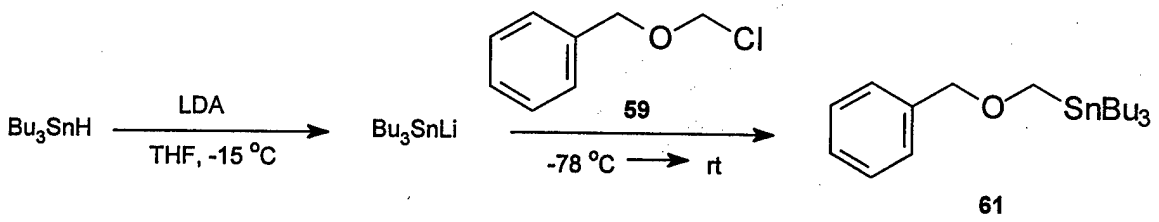
Table 1: Attempted Grignard Reagent Formation Conditions

Magnesium activation	Temperature (°C)	Electrophile
$HgCl_2$	-33	benzaldehyde
$HgCl_2$, 1,2-dibromoethane	-33	benzaldehyde
$HgCl_2$, 1,2-dibromoethane	0, -25, excess heat	piperonal
Mechanical	0	piperonal

The decomposition of the Grignard reagent, purportedly by two organometallic molecules reacting with one another to eliminate ethylene and two molecules of magnesium alkoxide[19], was never a result that could be substantiated by NMR. Nevertheless, all attempts at forming this Grignard reagent were unsuccessful.

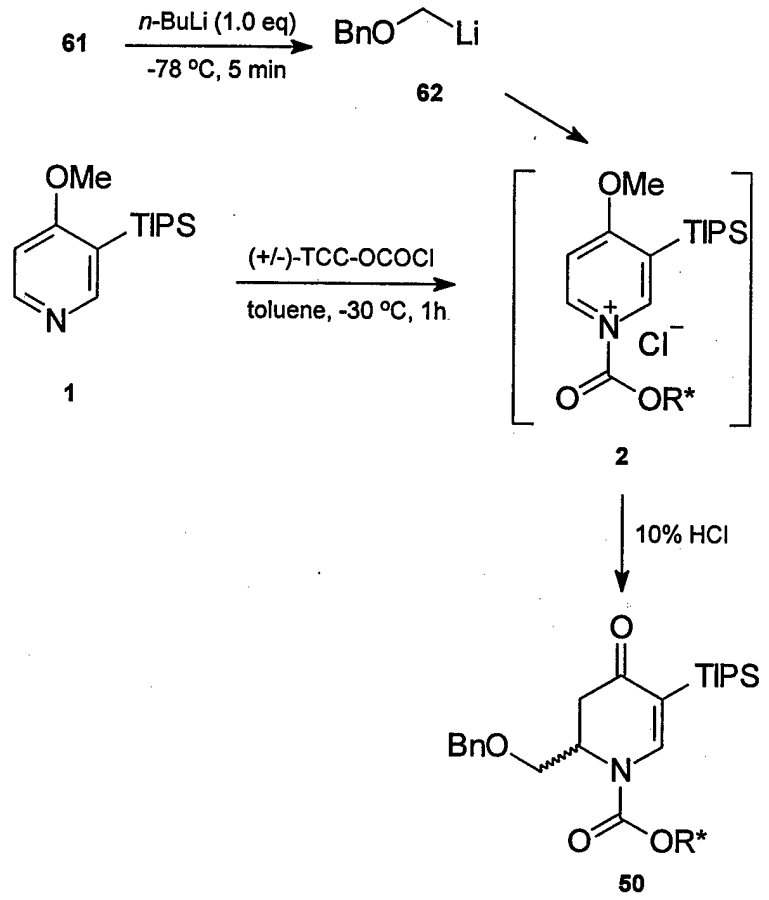
The use of a tributylstannane intermediate had been previously reported[20], and transmetallation to the lithium or cuprate reagent would prove successful. By Kaufman's procedure[20a], freshly distilled tributyltin hydride was deprotonated with LDA at –15 °C, cooled to –78 °C, and benzyl chloromethyl ether was added dropwise. The solution was warmed to room temperature, diluted with hexane, washed with brine, and concentrated. Vacuum distillation provided pure, anhydrous **61** in 80-87% yields, comparable to the literature.

Scheme 8: Formation of Tin Reagent



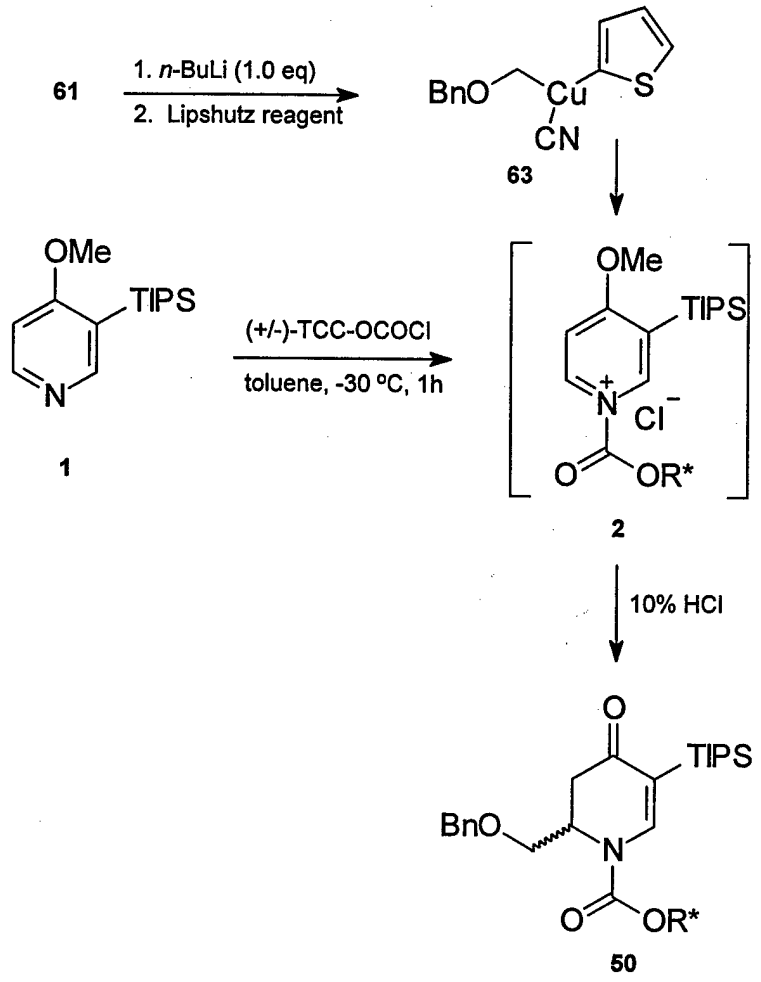
With the required tributylstannane **61** prepared, the next step was transmetallation and addition to the pyridinium salt. The first attempts were the addition of the organolithium reagent to the *N*-acylpyridinium salt. These early attempts were done using racemic auxiliary. By treatment of stannane **61** with *n*-BuLi at –78 °C, reagent **62** was formed and was then added to the *in situ* formed pyridinium salt. After hydrolysis, the reaction did produce some **50** in low yield (38%). To eliminate the possibility of thermal sensitivity, as was reportedly the case for the corresponding Grignard reagent, the pyridinium salt was transferred *via* double-tipped stainless steel needle to **62**. This "inverse addition" method showed no improvement over the "normal addition."

Scheme 9: Organolithium Addition to Pyridinium Salt



As was previously observed in the Comins' group[21], organolithiums are not the best organometallic reagents to use since they often attack the carbonyl of the carbamate instead of the C-2 position of the pyridinium salt. Therefore, the higher order cyanocuprate was next attempted. After forming **62** as previously described, lithium 2-thienylcyanocuprate (Lipshutz reagent[22]) was added, stirred for 5 min at –78 °C, and then was transferred to the pyridinium salt. This procedure (Scheme 10) proved successful after some optimization.

Scheme 10: Higher Order Cuprate Addition



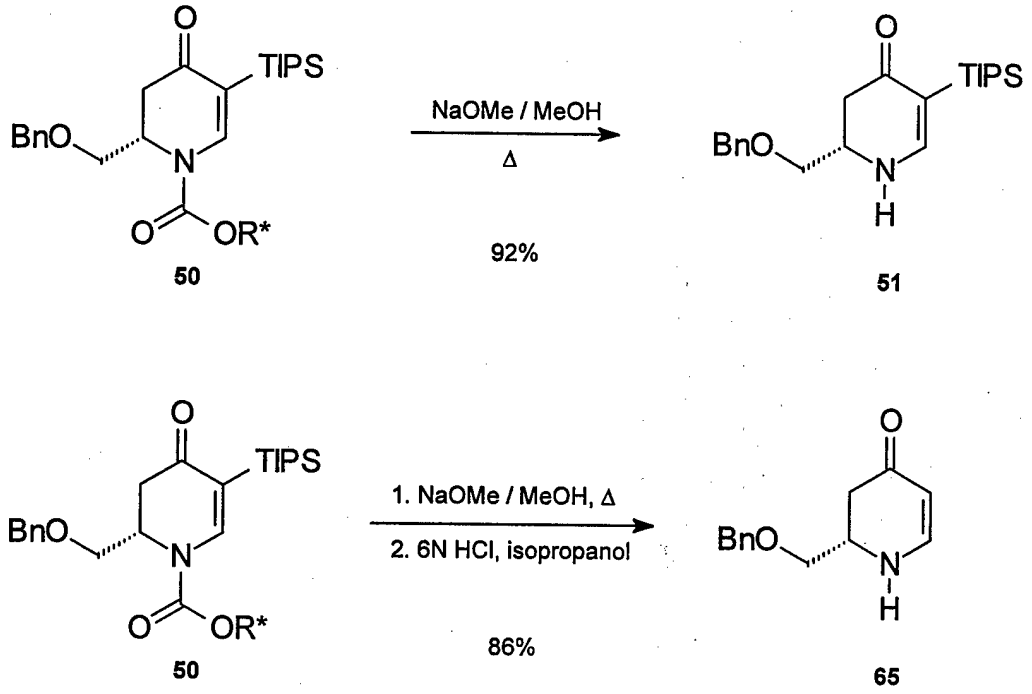
After allowing more time for both the organolithium and cuprate to form, consistent results were obtained and enantiopure chiral auxiliary was now used. Small-scale reaction yields ranged from 71-78%, with the major and minor diastereomers easily separated by radial PLC. HPLC analyses of the crude reaction mixtures determined that the diastereomeric excesses ranged from 79-82. These

de's are not as good as those typical of Grignard reagents, but are certainly sufficient.

Synthesis of (9*S*)- 8,8a-Dihydro-1*H*-oxazolo[3,4-α]pyridine-3,7-dione (54)

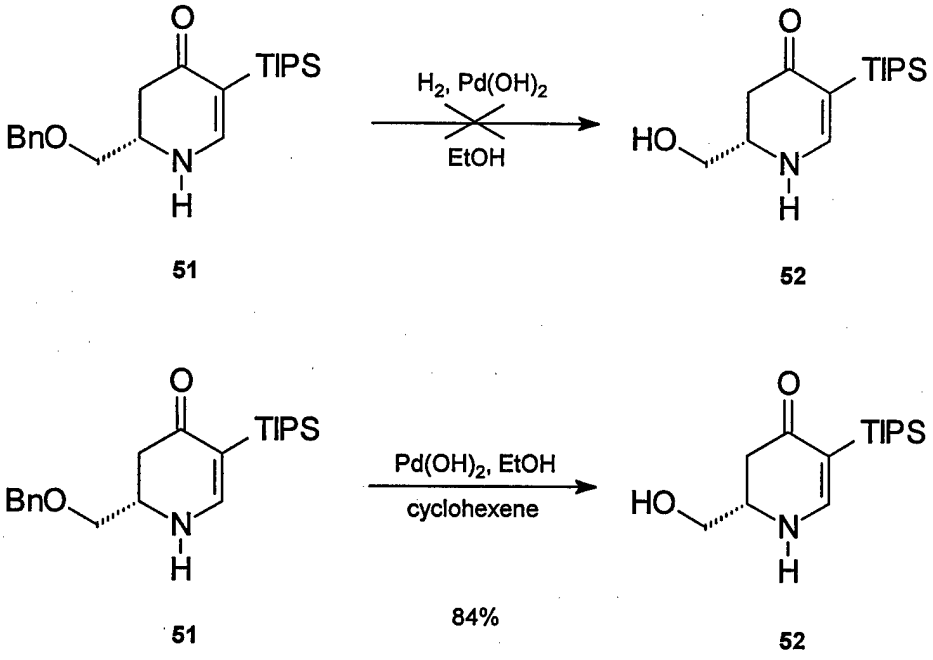
The next four transformations were focused on the synthesis of intermediate **54** (Scheme 6). The first of these transformations involved the removal of the chiral auxiliary, (-)-TCC alcohol, from **50**. Treatment with sodium methoxide in methanol for 18 h afforded free vinylogous amide **51** in excellent yield. A one-pot process removing both the chiral auxiliary and the TIPS group was also accomplished. After basic hydrolysis, protodesilylation occurred by treatment with excess hydrochloric acid in isopropanol to give **65** (Scheme 11).

Scheme 11: Removal of Chiral Auxiliary



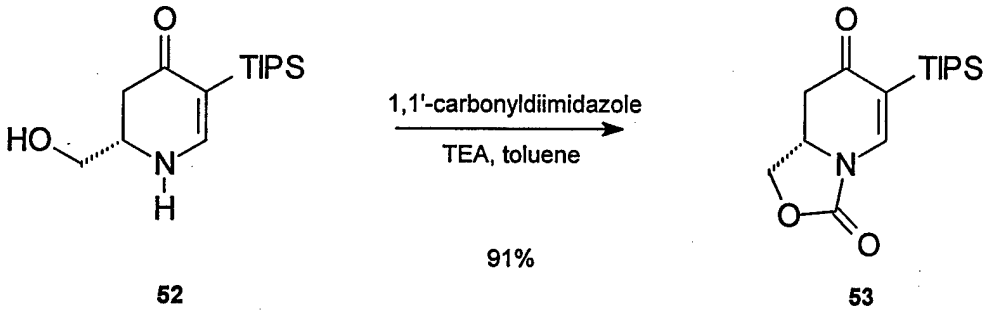
Compound **51** was next subjected to standard hydrogenolysis conditions, using palladium hydroxide, Pearlman's catalyst[23]. After several attempts, no reaction occurred, and catalytic transfer hydrogenolysis was performed using cyclohexene as the hydrogen donor[24] (Scheme 12). Excellent yields were obtained (84%), and this method would become the standard for debenzylation in this project.

Scheme 12: Hydrogenolysis



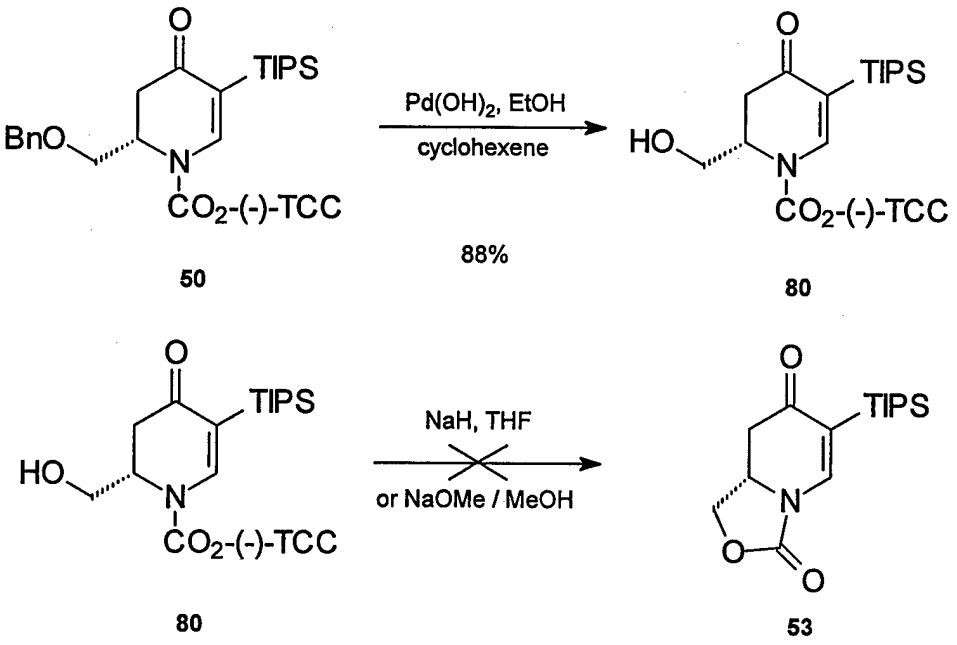
The next step in this segment was forming the bicyclic carbamate compound **53**. This was achieved by treatment of **52** with triethylamine and 1,1'-carbonyldiimidazole. This conversion yielded 91% of compound **53**.

Scheme 13: Bicyclic Carbamate Formation



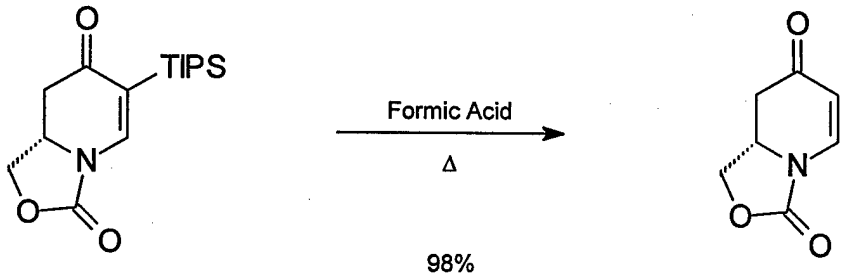
Before moving on, a shorter route to **53** was investigated. After debenzylating compound **50**, it was hoped that a deprotonated hydroxyl group would be nucleophilic enough to attack the carbamate carbonyl and displace the chiral auxiliary forming compound **53**. Catalytic transfer hydrogenation was performed in a manner similar to before producing compound **80** in high yield. Unfortunately, several attempts were made using both NaH (1.1 eq) and sodium methoxide. In both cases the major product was the deprotected-vinylogous amide, uncyclized compound **52**. In the latter case, using sodium methoxide, the yield of **52** was as high as 93%.

Scheme 14: Alternate Route to **53**



The final step of this segment was removing the TIPS group. Although it was easily removed along with the chiral auxiliary in Scheme 11, carrying the TIPS group through to this point simplified the purification of the products in Schemes 11, 12 & 13. The added non-polarity of the TIPS group balanced the highly polar free vinylogous amide and hydroxyl groups in this small molecule. Scheme 15 shows the ease with which protodesilylation occurred in refluxing formic acid. This step afforded compound **54** in near quantitative yield.

Scheme 15: Protodesilylation of **53**



53 **54**

C-3 Oxidation

Before the conjugate addition of the *n*-C_{12} side chain could be carried out, the hydroxyl group at C-3 needed to be installed. Several methods were attempted without success due to a lack of stereoselectivity.

Scheme 16 depicts the general plan for oxidation at C-3, using various bases to form the enolate and adding a source of electrophilic oxygen. Also shown in Table 2 are the conditions used in those attempts.

Scheme 16: Enolate Formation

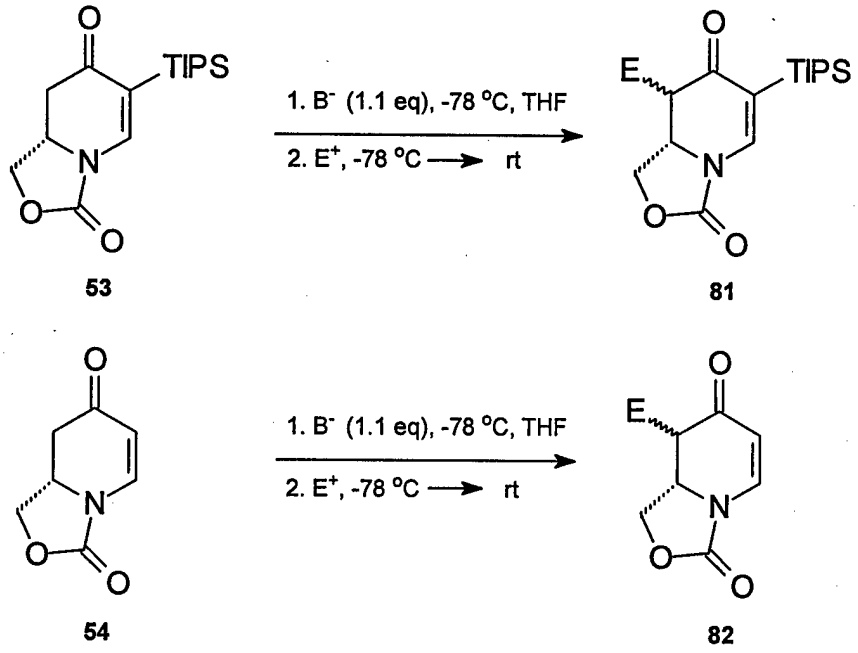


Table 2: Enolate Formation

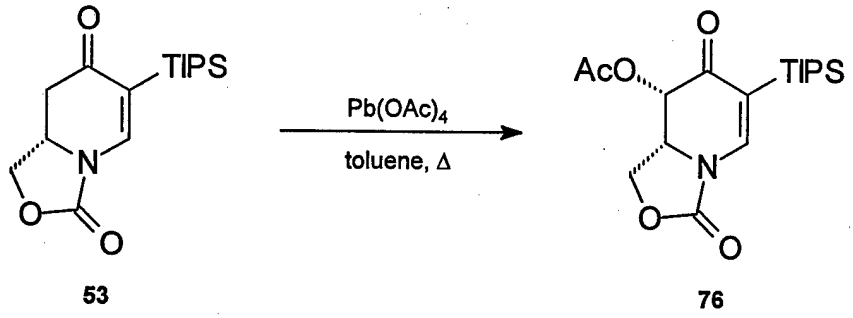
SM	Base	Electrophile	Result
53	LDA	MeI	Some methylation by NMR
53	LDA	$(Ph\text{-}CO_2)_2$	All SM
53	NaHMDS	$(Ph\text{-}CO_2)_2$	All SM
54	NaHMDS	$(Ph\text{-}CO_2)_2$	All SM
54	NaHMDS + $BF_3{\cdot}Et_2O$	$(Ph\text{-}CO_2)_2$	decomposition
54	NaHMDS	$(Me_3SiO)_2$	only 40% SM recovered

The first attempt at enolate formation seemed to work sufficiently; the NMR spectrum appeared to show some methylation. However, why each subsequent attempt failed, whether in enolate formation or in electrophilic substitution, could not be determined.

Previous work by the Comins' group[25] had shown that a more traditional method, using lead tetraacetate, was a low-yielding reaction and would produce the undesired *cis*-2,3 stereochemistry with this bicyclic system. This result was verified in attempts using these conditions (Scheme 17). Lead tetraacetate, acting in an axial attack fashion (see Figure 8), attacks from the bottom face leading to the undesired isomer **76**. The NMR spectrum of this product, isolated only in trace amounts, showed no visible coupling between the axial proton of C-2 and the lone

proton on C-3. The desired axial-axial orientation, as will be shown later, has a distinctly large coupling constant (J = 13.0 Hz).

Scheme 17: Acetoxylation of **53**



53 **76**

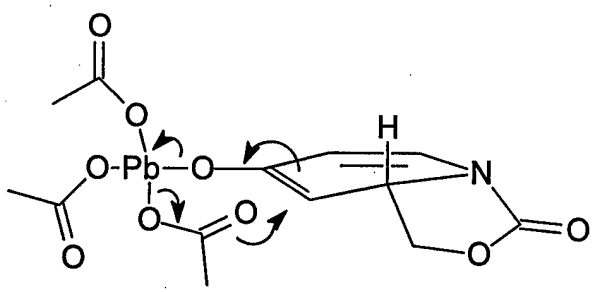


Figure 8: Axial Attack of $Pb(OAc)_4$

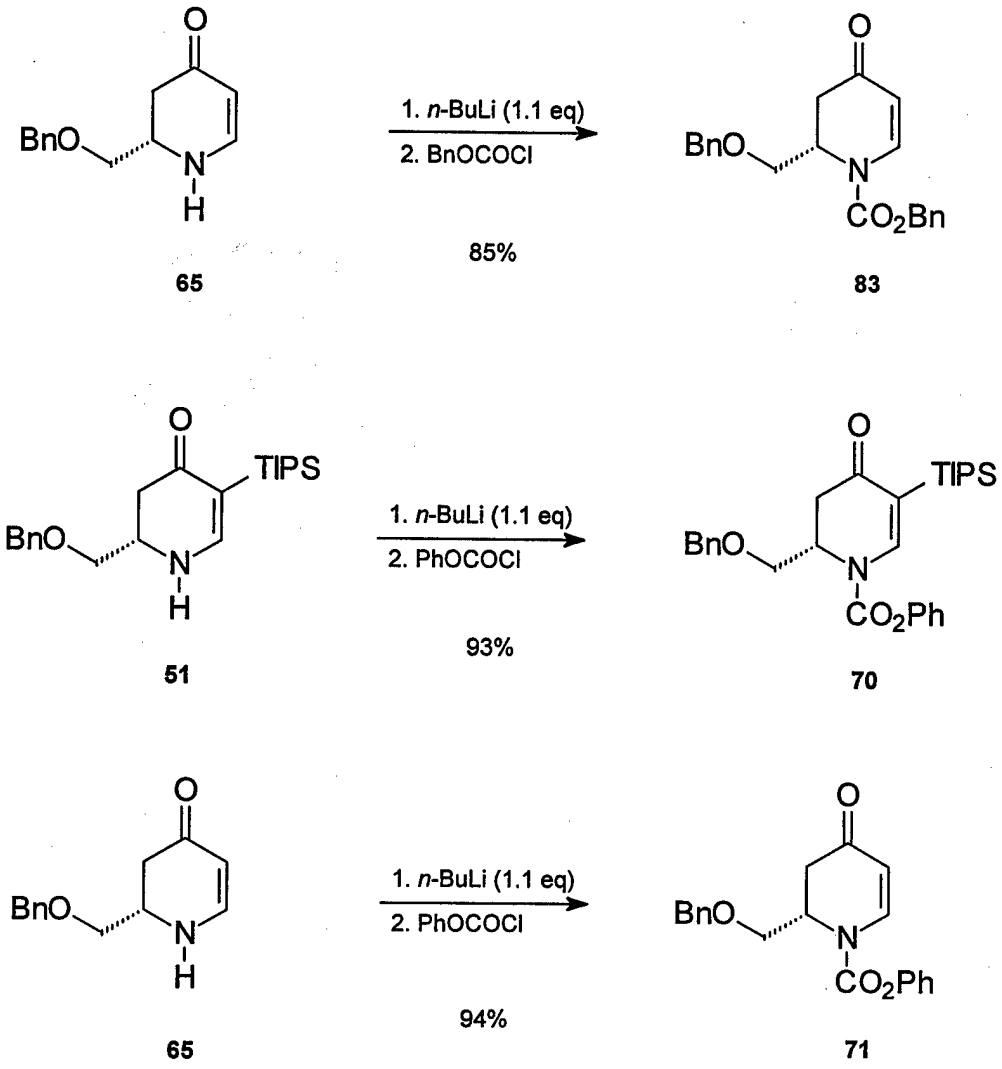
In order to take advantage of this stereoelectronic mode of attack and achieve the correct stereochemical outcome, the starting material must have the C-2 substituent in an axial position—as $A^{(1,3)}$ strain normally dictates in the monocyclic series. Therefore, the acetoxylation reaction needed to be carried out before cyclization of the carbamate ring.

This plan presented the problem of selecting the appropriate nitrogen protecting group. Earlier attempts at direct cyclization with the chiral auxiliary still attached had failed. Nevertheless, three separate paths would be explored varying the N-acyl group between benzyl, phenyl and (-)-TCC carbamates.

The benzyl carbamate was formed by treatment of **65** with *n*-BuLi and then benzyl chloroformate giving **83** in high yield (80%). Similarly, the phenyl carbamates **70** and **71** (Method B) were formed using **51** and **65** as the respective starting materials (Scheme 18).

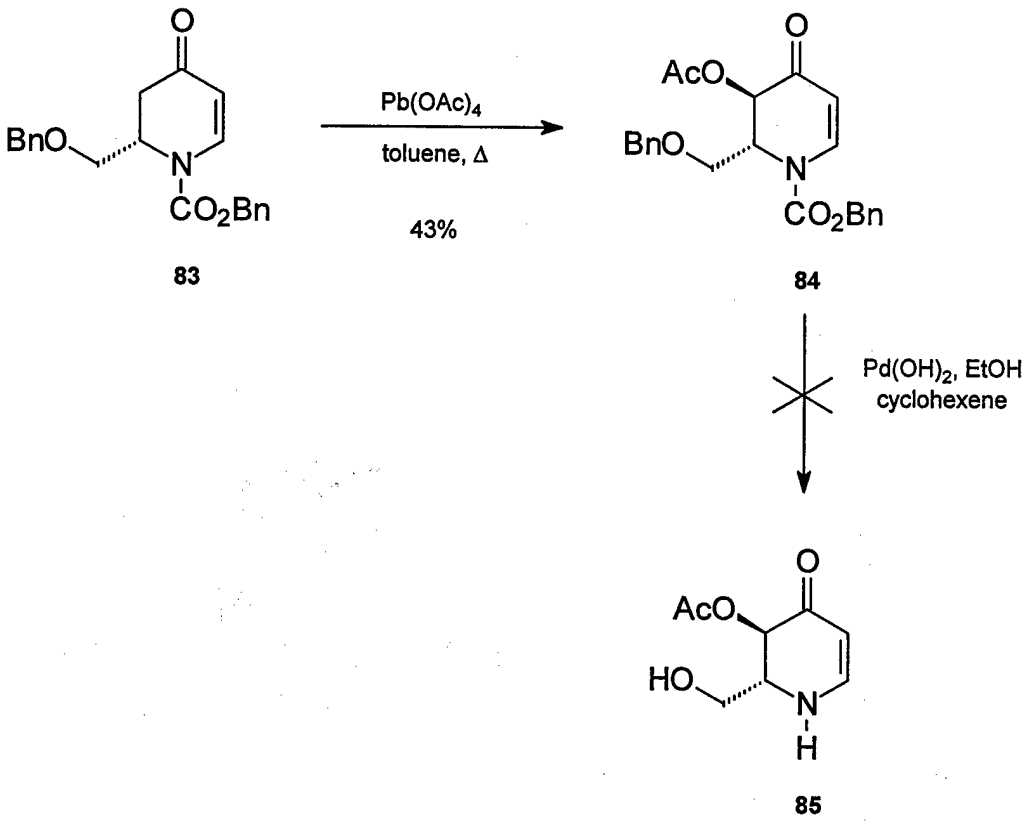
Starting with the benzyl carbamate **83**, acetoxylation in a manner similar to previous reactions[25] was carried out in refluxing anhydrous toluene with $Pb(OAc)_4$, freshly recrystallized from acetic acid, dried under vacuum, and stored in a glove box. This reaction afforded compound **84** in only moderate yield (43%) (Scheme 19). Before any optimization was done, the product was immediately subjected to catalytic transfer hydrogenation. The failure of this step was most likely due to some instability of the product, since all the starting material was consumed but only decomposition was observed.

Scheme 18: Varying the N-Acyl groups



65 **83** **51** **70** **65** **71**

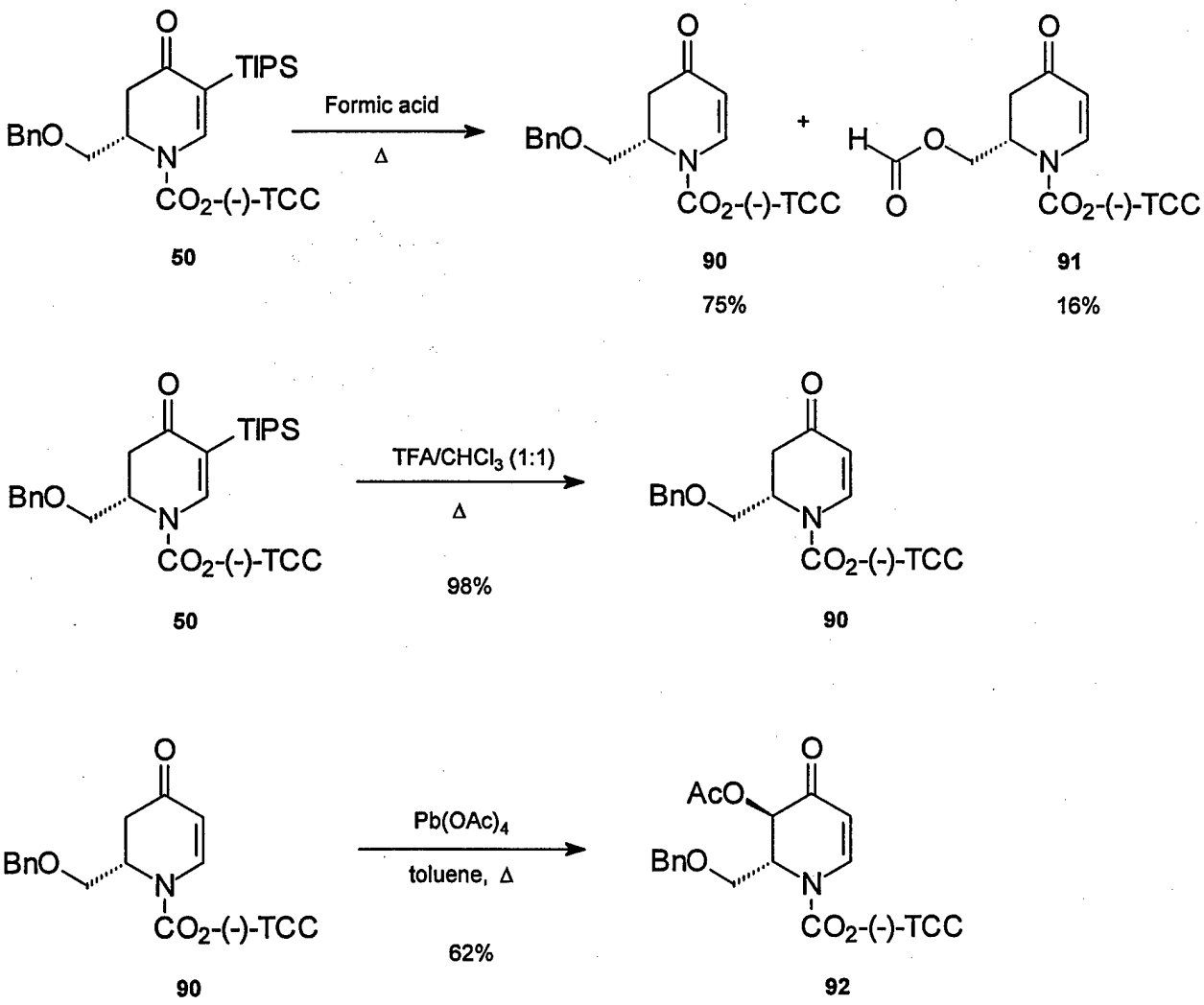
Scheme 19: Progress with the Benzyl Carbamate



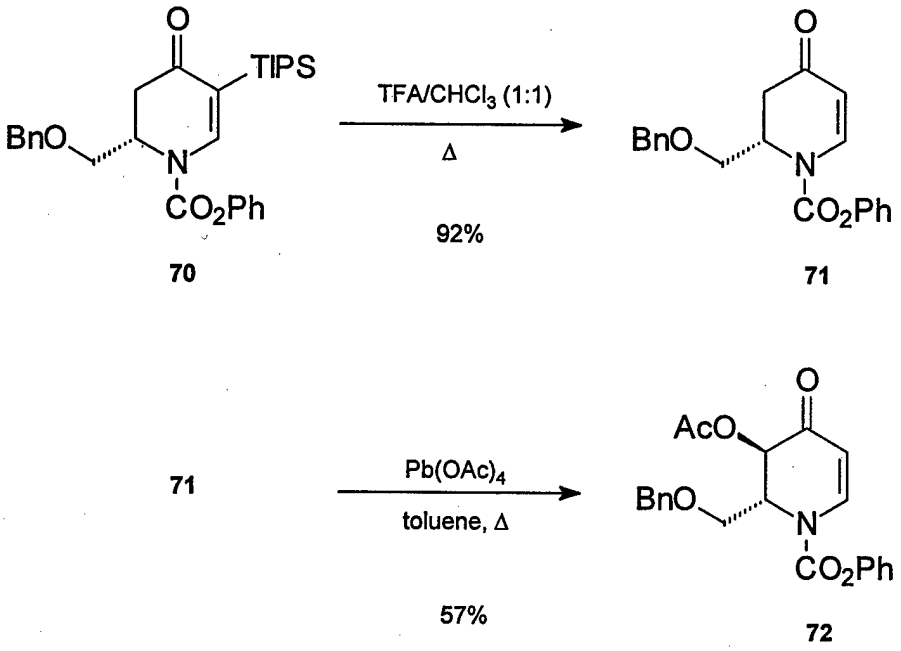
Next, the (-)-TCC carbamate series was carried out. Protodesilylation, using formic acid as previously described, afforded compound **90** in 75% yield. However, there was a significant amount (16%) of a byproduct—the debenzylated, formate ester **91** (Scheme 20). Changing from formic to trifluoroacetic acid, with an equal amount of $CHCl_3$, alleviated the formation of byproduct **91** and provided **90** in 98% yield. When compound **90** was subjected to the lead tetraacetate procedure, a good

yield (62%) of **92** was obtained. Unfortunately, the previous failure to form the bicyclic ring (Scheme 14) left little optimism for the cyclization of compound **92**.

Scheme 20: Progress with the (-)-TCC Carbamate



Scheme 21: Progress with the Phenyl Carbamate



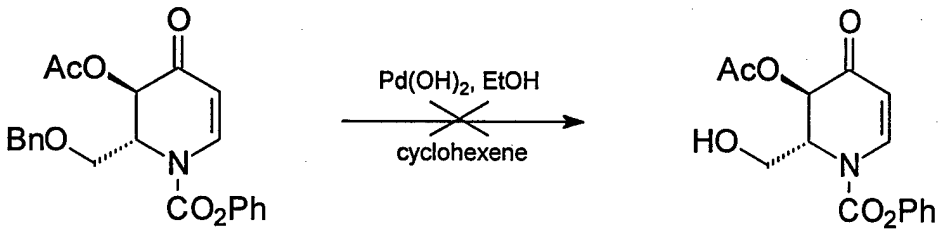
With the last hope, the phenyl carbamate series, compound **70** was desilylated using TFA to produce **71** (Method A) in excellent yield. This product was carried on to acetoxylation, where optimization of the conditions was successful in preparing **72** in 57% yield. Variations in these conditions are shown in Table 3.

Table 3: Conditions for the Acetoxylation of **71**

SM	Eq of $Pb(OAc)_4$	Time	Solvent	Result
71	3.6	24h	toluene	57% yield & 24% SM
71	2.6	20h	trifluorotoluene	47% yield & 26% SM
71	2.6	14h	toluene	53% yield & minimal SM
71	2.6	14h	toluene	56% yield & minimal SM

The final hurdle in the formation of this key intermediate was the debenzylation of **72**. It was speculated that cyclization to compound **73** would be a simple task with the free hydroxyl group. Catalytic transfer hydrogenolysis, in a situation similar to Scheme 18, was unfortunately unsuccessful with the complete consumption of starting material but no recognizable product.

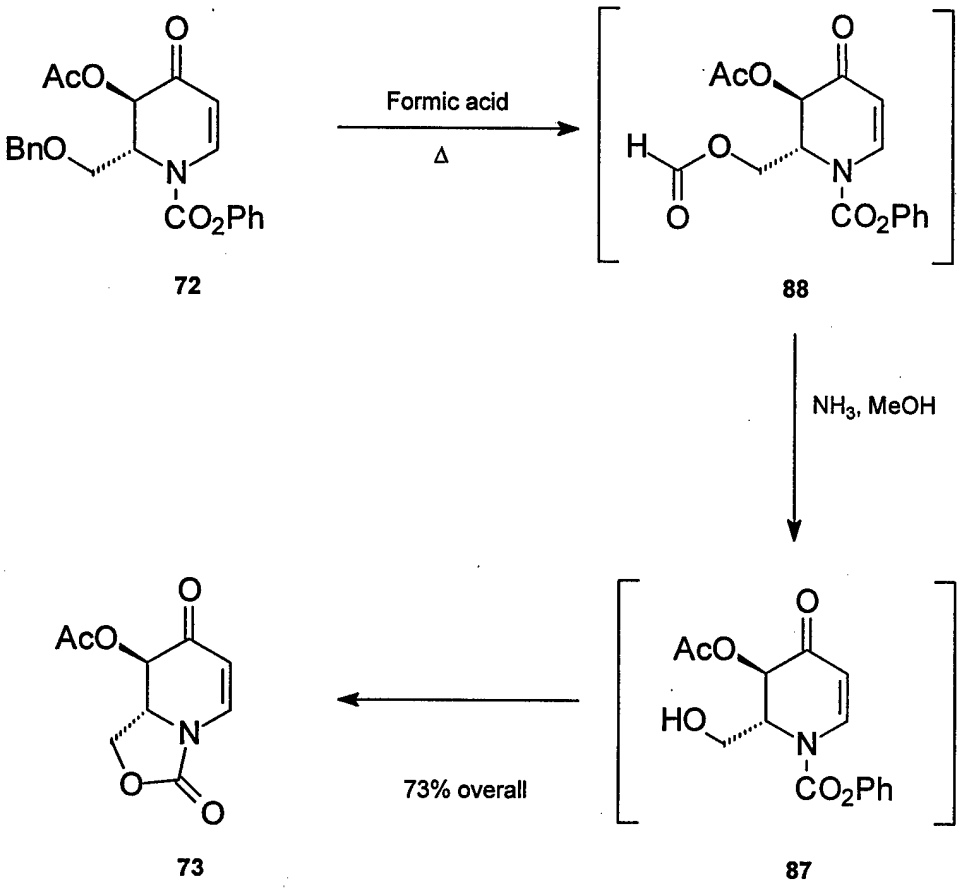
Scheme 22: Failed Hydrogenolysis of **72**



72 **87**

The formate ester, a previously undesirable byproduct, would prove to be a useful intermediate. By refluxing **72** in formic acid for several hours, spot-to-spot conversion of the benzyl ether to formate ester was accomplished. After concentrating the solution *in vacuo*,, and again refluxing the crude material in methanol, none of intermediate **87** was found. Instead, a small amount of the desired cyclized compound **73** was isolated. It was evident that the cyclization step was spontaneous under these conditions. Unfortunately, no matter how long the solution was refluxed in methanol, only a small portion of the formate ester would cleave. Therefore, more harsh conditions were necessary, and so methanolic ammonia was used. In order to control the speed of the reaction, since ammonia also cleaves the acetate (formate esters are cleaved ~100 times faster than acetate esters[26]), the crude formate ester in methanol solution was cooled to 0 °C before adding the ammonia. After complete cleavage of the formate, the ammonia could be quenched with acetic acid before the acetate was harmed. This technique afforded a good yield (73%) of the desired acetoxylated bicyclic intermediate 73 (Scheme 23).

Scheme 23: Debenzylation / Spontaneous Cyclization



72 88 87 73

Attempted Synthesis of (+)-Desoxoprosopinine

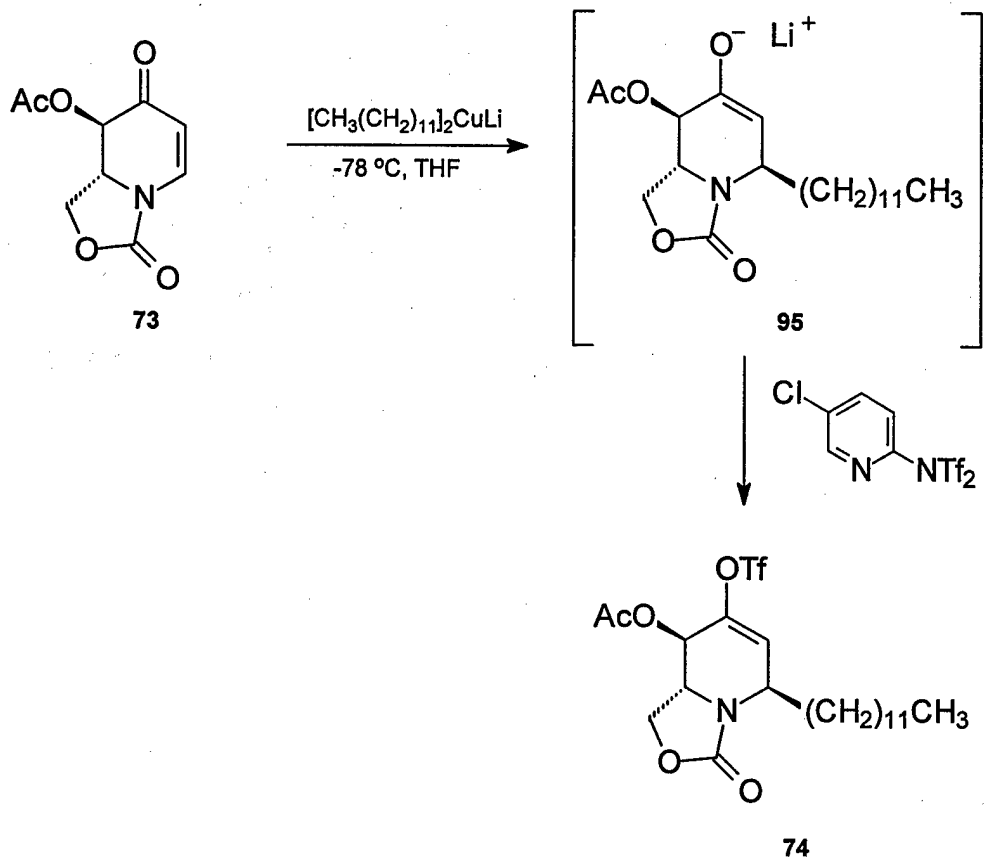
Compound **73** is a potential stepping stone en route to many of the *Prosopis* alkaloids. By 1,4-addition of the corresponding predesigned side-chain, *prosopine* **5**, *prosopinine* **6**, and *prosopinone* **7** are all within reach. In order to demonstrate this in the most simplified way, the synthesis of (+)-desoxoprosopinine **10** was attempted. Although not a natural product, the synthesis of **10** would stand as a model for these alkaloids without having to expend the effort of designing and synthesizing the various side chains.

Using commercially available 1-iodododecane, a dialkylcuprate was formed by transmetallation of the corresponding lithium reagent with copper(I) bromide-dimethyl sulfide complex. This copper(I) complex is reasonably stable, readily available, and easily purified. By treatment of the alkyl iodide with *t*-BuLi, lithium-halogen exchange is performed, and then that solution is transferred to a solution of the copper complex. Once the cuprate is completely formed, the dropwise addition of compound **73** affords intermediate **95** (Scheme 24) with complete stereochemical control.

Since none of the target compounds, including (+)-desoxoprosopinine, have any substitution at the C-4 position, trapping of this enolate as the vinyl triflate and subsequent reduction was potentially an efficient method of removing that C-4 functionality. Addition of a triflating reagent developed by the Comins' group[5c], 2-[*N,N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine, effectively trapped the

lithium enolate as the vinyl triflate **74**. This complete transformation was effected in good overall yield (60%).

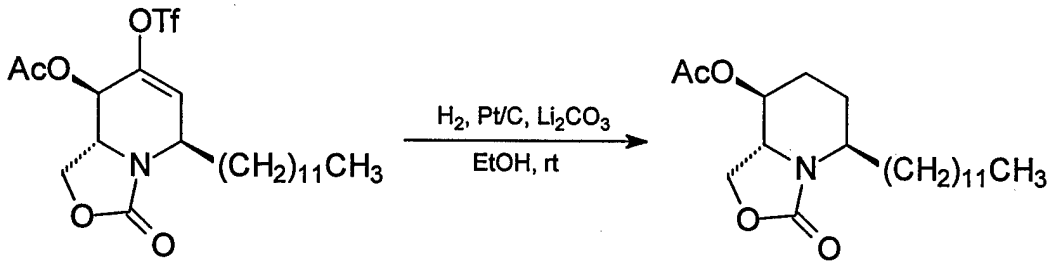
Scheme 24: Conjugate Addition to **73**



73 **95** **74**

Reduction of vinyl triflate **74** with platinum on carbon under a balloon pressure of hydrogen using lithium carbonate as an acid scavenger produced compound **75** in excellent yield (Scheme 25).

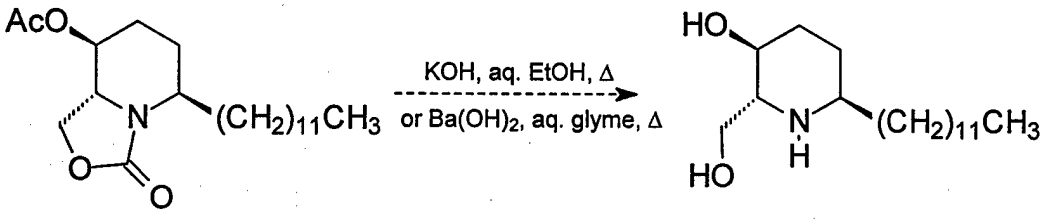
Scheme 25: Reduction of the Vinyl Triflate **74**



74 **75**

In order to complete the synthesis of (+)-desoxoprosopinine, deprotection of the C-3 hydroxyl group and hydrolysis of the 5-membered carbamate ring must be accomplished. Many different conditions are possible for such a transformation, and two of those possibilities are depicted in Scheme 26. To date, this step has not been successfully carried out, but future efforts should produce the desired transformation.

Scheme 26: Synthesis of (+)-Desoxoprosopinine

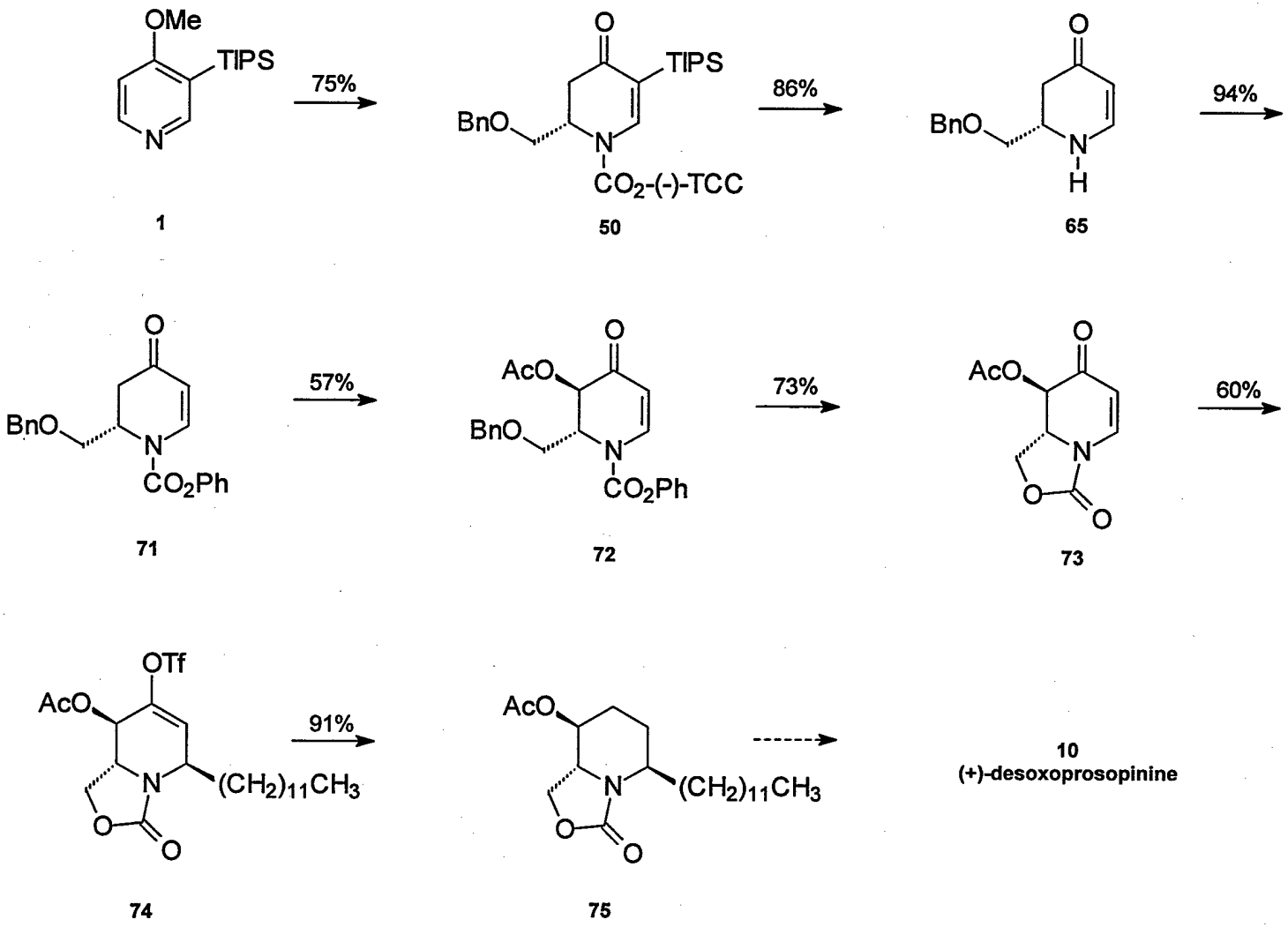


75 **10**

Conclusions

Although the final target, (+)-desoxoprosopinine was not reached, the utility of chiral *N*-acyl-2,3-dihydro-4-pyridones in the asymmetric synthesis of *Prosopis* alkaloids has been demonstrated. The piperidine ring structure has been established with excellent stereochemical control. The ability to use intermediate **73** as a turning point en route to many different *Prosopis* alkaloids is novel. With more time and effort, the final ring opening step should be accomplished, completing this model synthesis. As shown in Scheme 27, the final synthetic route utilized 7 steps to arrive at intermediate **75** with a overall yield of 13.8%.

Scheme 27: Final Synthetic Route



Experimental Section

All reactions described in this section were performed using oven-dried glassware under an argon or dry nitrogen atmosphere. THF, toluene, and diethyl ether were dried by distillation from sodium/benzophenone. Other reagents and solvents were stored over molecular sieves under argon and used directly. Radial PLC was done using a model 7924T Chromatotron (Harrison Research, Palo Alto, CA) using thin-layers of Silica Gel-Gypsum. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. High resolution mass spectra were taken using a JEOL HX1110HF mass spectrometer by the NCSU Mass Spectrometry Facility. Infrared spectra were obtained on a Perkin-Elmer 7500 spectrometer. Melting points were measured using a Thomas-Hoover capillary melting point apparatus. NMR spectra were taken using both a Varian XL-300 and a GE GN 300 spectrometer. Optical rotations were measured with a Randolf Research (Flanders, NJ) Autopol III automatic polarimeter using a 1.0 dm cell. Waters and Associates HPLC systems used for both diastereomeric and enantiomeric excess measurements were: (1) a 600E multisolvent pump, with a 486 tunable detector and a μ-PORASIL analytical column; and (2) a 501 pump, with a 440 absorbance detector with a Chiralcel OJ column.

(2*S*)-1-[(1*R*,2*S*)-*trans*-2-(α-Cumyl)cyclohexyloxycarbonyl]-2-(benzyloxymethyl)-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (50). To a stirred solution of **61** (308 mg, 0.75 mmol) in THF cooled to –78 °C was added 0.375 mL *n*-butyllithium (2.0 M solution in hexanes). After stirring for 30 min at the same temperature, 3.0 mL of lithium 2-thienylcyanocuprate (0.25 M solution in diethyl ether) was added dropwise. This solution was allowed to stir for an additional 30 min at –78 °C. In a separate flask, a stirred solution of **1** (132.8 mg, 0.50 mmol) in toluene was cooled to –30 °C, and 0.52 mL of (-)-TCC chloroformate (1.0 M solution in toluene) was added dropwise. This solution was allowed to stir at –30 °C for 1 h, and then was cooled to –78 °C. Through a double-tipped stainless steel needle, surrounded by a layer of dry ice, the cuprate solution was slowly transferred to the pyridinium salt solution. The resulting mixture was stirred for 1 h, at which point TLC showed complete disappearance of starting material **1.** The reaction was then quenched with an excess of 10% aqueous hydrochloric acid. This acid hydrolysis step was stirred for 1 h. The solution was then diluted with EtOAc, washed with water and brine. The combined aqueous layers were back-extracted twice with EtOAc, and the combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. Purification by radial PLC (2-10% EtOAc/hexanes) yielded a colorless oil which solidified upon standing. Recrystallization from methanol afforded 215 mg (70%) of **50** as a white solid, (mp 84-85 °C). A small amount (16 mg, 5%) of the minor diastereomer was also isolated, for a total yield of 75%. HPLC analysis of the crude reaction mixture

determined a de of 82; $[\alpha]^{23}_D$ –30.9 (*c* 0.12, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.10-7.31 (m, 10H), 4.79 (m, 1H), 4.32 (s, 2H), 2.97-3.10 (m, 2H), 2.40 (m, 1H), 2.18 (m, 2H), 2.00 (m, 1H), 1.61-1.74 (m, 4H), 1.17-1.35 (m, 9H), 0.99-1.04 (m, 22H); ^{13}C (75 MHz, $CDCl_3$) δ 196.2, 152.5, 152.2, 147.7, 137.7, 128.4, 128.0, 127.9, 127.7, 125.2, 110.1, 77.8, 73.0, 58.4, 51.0, 50.9, 39.4, 38.1, 33.1, 30.8, 26.7, 25.8, 24.6, 21.5, 18.9, 11.2; IR (thin film, NaCl) 2942, 2863, 1716, 1659, 1577, 1453, 1383, 1325, 1264 cm^{-1}. Anal. Calcd for $C_{38}H_{55}NO_4Si$: C, 73.86; H, 8.97; N, 2.27. Found C, 73.92; H, 9.17; N, 2.34. HRMS calcd for $C_{38}H_{56}NO_4Si$ 618.3979 $[M + H]^+$, found 618.3986.

(2*S*)-2-(Benzyloxymethyl)-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (51). To a stirred solution of **50** (3.525 g, 5.704 mmol) in 250 mL of MeOH was added 13.0 mL of sodium methoxide (4.36 M solution in MeOH). The solution was heated to reflux, and the reaction was stirred for 18 h. The reaction mixture was cooled to rt and glacial acetic acid was added until the solution reached a pH of 7. The solution was concentrated *in vacuo*, and the resulting sodium acetate precipitate was washed with EtOAc and removed by filtration through Celite®. Concentration *in vacuo*, purification by radial PLC (5-20% EtOAc/hexanes), and recrystallization from hexanes gave 1.962 g (92%) of **51** as a white solid, mp 109-110 °C; $[\alpha]^{23}_D$ +201.3 (*c* 1.02, MeOH); ^1H (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 7.16 (d, 1H, *J* = 6.3 Hz), 5.48 (br s, 1H), 4.58 (d, 1H, *J* = 11.8 Hz), 4.52 (d, 1H, *J* = 11.8 Hz), 3.90 (m, 1H), 3.54 (m, 2H), 2.33 (m, 2H), 1.26 (m, 3H), 1.02 (t, 18H, *J* = 7.1 Hz); ^{13}C (75

MHz, $CDCl_3$) δ 195.2, 155.8, 137.5, 128.6, 128.1, 127.8, 100.2, 73.5, 71.8, 52.4, 39.3, 18.9, 11.3; IR (thin film, NaCl) 3279, 2930, 2849, 1604, 1552, 1499, 1459, 1360, 1307, 1156, 883 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO_2Si$: C, 70.73; H, 9.44; N, 3.75. Found C, 70.61; H, 9.59; N, 3.85.

(2*S*)-2-(Hydroxymethyl)-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (52). To a stirred solution of **51** (299 mg, 0.800 mmol) in 20 mL of EtOH was added 367 mg of 20% $Pd(OH)_2/C$ and 5 mL of cyclohexene. The solution was heated to reflux and stirred for 24 h. The reaction mixture was then cooled to rt, filtered through Celite® with EtOAc, and concentrated *in vacuo*. Purification by radial PLC (50-75% EtOAc/hexanes) gave 190 mg (84%) of **52** as a white solid, mp 129.0-129.5 °C; $[\alpha]^{23}_D$ +255.4 (*c* 0.65, MeOH); ^1H (300 MHz, $CDCl_3$) δ 7.21 (d, 1H, *J* = 6.3 Hz), 5.66 (br s, 1H), 3.78 (m, 2H), 3.66 (t, 1H, *J* = 10.0 Hz), 2.36 (m, 2H), 2.17 (br s, 1H), 1.26 (m, 3H), 1.03 (t, 18H, *J* = 6.9 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 195.6, 156.1, 100.1, 64.4, 54.2, 39.0, 18.9, 11.3; IR (thin film, NaCl) 3389, 3212, 2931, 2861, 1608, 1572, 1549, 1461, 1361, 1314, 1155, 1044, 879 cm^{-1}. Anal. Calcd for $C_{15}H_{29}NO_2Si$: C, 63.55; H, 10.31; N, 4.94. Found C, 63.38; H, 10.47; N, 4.89.

(9*S*)-6-(Triisopropylsilyl)- 8,8a-dihydro-1*H*-oxazolo[3,4-α]pyridine-3,7-dione (53). To a stirred solution of **52** (300 mg, 1.06 mmol) in 40 mL of toluene was added Et_3N (0.30 mL, 2.0 mmol) and 1,1′-carbonyldiimidazole (205.9 mg, 1.270

mmol). The solution was heated to reflux and stirred for 16 h. The reaction mixture was cooled to rt and then concentrated *in vacuo*. Purification by radial PLC (20-50% EtOAc/hexanes) and recrystallization from EtOAc/hexanes gave 298 mg (91%) of **53** as a white solid, mp 152.0-152.8 °C; $[\alpha]^{23}_{D}$ +270.0 (*c* 1.10, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 4.71 (t, 1H, *J* = 8.1 Hz), 4.45 (m, 1H), 4.13 (t, 1H, *J* = 9.5 Hz), 2.71 (dd, 1H, *J* = 4.5 Hz, *J* = 15.2 Hz), 2.58 (t, 1H, *J* = 14.9 Hz), 1.32 (m, 3H), 1.05 (m, 18H); ^{13}C (75 MHz, $CDCl_3$) δ 194.8, 152.4, 144.0, 113.5, 69.0, 52.4, 40.9, 18.9, 11.1; IR (thin film, NaCl) 2946, 2863, 1760, 1658, 1575, 1388, 1269, 1196, 1072, 984, 880 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.79; N, 4.53. Found C, 61.83; H, 8.77; N, 4.54.

(9*S*)- 8,8a-Dihydro-1*H*-oxazolo[3,4-α]pyridine-3,7-dione (54). A solution of **53** (101 mg, 0.326 mmol) in formic acid was heated to reflux and stirred for 1.5 h. The reaction mixture was cooled to rt and then concentrated *in vacuo*. Purification by radial PLC (60-100% EtOAc/hexanes) and recrystallization from EtOAc/hexanes gave 49 mg (98%) of **54** as a white solid, mp 141.2-142.0 °C; $[\alpha]^{23}_{D}$ +443.9 (*c* 0.31, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* = 7.9 Hz), 5.51 (d, 1H, *J* = 7.9 Hz), 4.72 (t, 1H, *J* = 8.2 Hz), 4.45 (m, 1H), 4.13 (t, 1H, *J* = 9.4 Hz), 2.72 (dd, 1H, *J* = 4.6 Hz, *J* = 16.0 Hz), 2.57 (t, 1H, *J* = 15.4 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 190.9, 152.3, 138.6, 109.3, 69.0, 52.6, 40.2; IR (thin film, NaCl) 1776, 1656, 1601, 1443, 1385, 1368, 1320, 1278, 1260, 1179, 1099, 987, 750 cm^{-1}. Anal. Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found C, 55.20; H, 4.60; N, 8.96.

(2*S*)-2-(Benzyloxymethyl)-2,3-dihydro-4-pyridone (65). To a stirred solution of **50** (200 mg, 0.324 mmol) in MeOH was added 0.74 mL of sodium methoxide (4.36 M solution in MeOH). The solution was heated to reflux, and the reaction was stirred for 18 h. The reaction mixture was cooled to rt and 6N HCl in isopropanol was added dropwise until the solution reached a pH of 1. This solution was allowed to stir at room temperature for 1.25 h, after which the pH was returned to 7 by the slow addition of solid Na_2CO_3. The solution was concentrated *in vacuo*, and the resulting solid was dissolved in EtOAc and filtered through Celite®. Concentration *in vacuo*, purification by radial PLC (50-100% EtOAc/hexanes), and recrystallization from hexanes gave 60 mg (86%) of **65** as a white solid, mp 107.8-108.3 °C; $[\alpha]^{23}_D$ +285.3 (*c* 0.38, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 7.30-7.40 (m, 5H), 7.16 (d, 1H, *J* = 7.0 Hz), 5.34 (br s, 1H), 5.02 (d, 1H, *J* = 7.5 Hz), 4.56 (s, 1H), 3.92 (m, 1H), 3.56 (m, 2H), 2.34 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 191.7, 150.8, 137.4, 128.6, 128.1, 127.9, 99.5, 73.5, 71.6, 52.8, 38.4; IR (thin film, NaCl) 3255, 3036, 2858, 1619, 1572, 1447, 1405, 1348, 1217, 1170, 1092 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found C, 71.58; H, 6.92; N, 6.37.

(2*S*)-2-(Benzyloxymethyl)-1-(phenoxycarbonyl)-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (70). To a solution of **51** (198 mg, 0.530 mmol) in 15 mL THF, cooled to –78 °C, was added 0.22 mL *n*-butyllithium (2.53 M solution in

hexanes), and the mixture was stirred for 20 min. Phenyl chloroformate (0.07 mL, 0.56 mmol) was added, and the solution was stirred for 30 min. The reaction was quenched with saturated $NaHCO_3$ and then warmed to rt. The solution was extracted with EtOAc, washed with water (3x), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by radial PLC (5-10% EtOAc/hexanes) afforded 240 mg (93%) of **70** as a colorless oil: $[\alpha]^{23}_D$ –49.1 (*c* 2.05, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.24-7.40 (m, 8H), 7.07 (br s, 2H), 4.93 (m, 1H), 4.52 (q_{AB}, 2H, *J* = 12.1 Hz), 3.62 (m, 2H), 2.95 (dd, 1H, *J* = 7.2 Hz, *J* = 16.3 Hz), 2.62 (d, 1H, *J* = 16.2 Hz), 1.31 (m, 3H), 1.05 (t, 18H, *J* = 8.2 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 195.9, 150.8, 146.9, 137.7, 129.7, 128.7, 128.0, 126.4, 121.5, 112.6, 73.6, 68.9, 53.0, 38.5, 19.0, 11.4; IR (thin film, NaCl) 2941, 2859, 1739, 1662, 1580, 1494, 1315, 1246, 1201, 1156, 1099, 1021 cm^{-1}. Anal. Calcd for $C_{29}H_{39}NO_4Si$: C, 70.55; H, 7.96; N, 2.84. Found C, 70.41; H, 7.87; N, 2.79.

(2*S*)-2-(Benzyloxymethyl)-1-(phenoxycarbonyl)-2,3-dihydro-4-pyridone (71). **Method A:** To a solution of **70** (175 mg, 0.354 mmol) in 10 mL of $CHCl_3$ was added 10 mL TFA. The solution was heated to reflux and stirred for 6 h. The reaction mixture was cooled to rt and then concentrated *in vacuo*. Purification by radial PLC (10-20% EtOAc/hexanes) afforded 110 mg (92%) of **71** as a colorless oil: $[\alpha]^{23}_D$ –44.4 (*c* 2.17, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 7.88 (d, 1H, *J* = 8.0 Hz), 7.21-7.38 (m, 8H), 7.05 (m, 2H), 5.39 (d, 1H, *J* = 8.2 Hz), 4.95 (m, 1H), 4.51 (q_{AB}, 2H, *J* = 11.9 Hz), 3.72 (m, 1H), 3.60 (m, 1H), 2.92 (dd, 1H, *J* = 6.9 Hz, *J* = 16.6 Hz),

2.62 (d, 1H, J = 16.8 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 192.4, 151.5, 150.6, 141.7, 137.6, 129.6, 128.6, 127.9, 127.8, 126.4, 121.4, 108.0, 73.5, 68.5, 52.9, 37.5; IR (thin film, NaCl) 3064, 2864, 1738, 1674, 1608, 1495, 1455, 1423, 1331, 1269, 1190, 1103, 1027, 914, 744, 690 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found C, 71.19; H, 5.67; N, 4.08.

Method B: To a solution of **65** (16 mg, 0.0736 mmol) in 1.0 mL of THF, cooled to –78 °C, was added 0.03 mL *n*-butyllithium (2.5 M solution in hexanes), and the mixture was stirred for 20 min. Phenyl chloroformate (0.010 mL, 0.078 mmol) was added, and the solution was stirred for 30 min. The reaction was quenched with saturated $NaHCO_3$ and then warmed to rt. The solution was extracted with EtOAc, washed with water (3x), dried over $MgSO_4$, and concentrated *in vacuo*. By the same purification in Method A, 23.2 mg (94%) of **71** was isolated.

(2*R*, 3*R*)-3-Acetoxy-2-(benzyloxymethyl)-1-(phenoxycarbonyl)-2,3-dihydro-4-pyridone (72). To a flask containing **71** (27 mg, 0.080 mmol) under a dry nitrogen atmosphere was added $Pb(OAc)_4$ (92 mg, 0.21 mmol, freshly recrystallized from glacial acetic acid and dried *in vacuo*). The flask was sealed under nitrogen, and the reaction mixture was dissolved in 15 mL of toluene, heated to reflux and stirred for 18h. By TLC, the reaction was not complete, yet no active $Pb(OAc)_4$ seemed to be present, so additional $Pb(OAc)_4$ (35 mg, 0.080 mmol) was added and refluxing was resumed for another 6 h. After cooling to rt, the solution was filtered through silica gel with EtOAc and then concentrated *in vacuo*. Purification by radial PLC

(20% EtOAc/hexanes) gave 18 mg (57%) of **72** as a colorless oil: $[\alpha]^{23}_D$ +88.5 (*c* 2.055, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 8.03 (d, 1H, *J* = 8.4 Hz), 7.25-7.42 (m, 10H), 7.07 (m, 2H), 5.50 (d, 1H, *J* = 8.6 Hz), 5.29 (s, 1H), 4.91 (br s, 1H), 4.53 (s, 2H), 3.77 (m, 2H), 2.14 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 186.6, 169.6, 150.5, 142.7, 137.3, 129.8, 128.7, 128.1, 127.9, 126.7, 121.4, 106.5, 73.7, 70.1, 67.5, 58.1, 21.2; IR (thin film, NaCl) 3076, 2920, 2858, 1745, 1677, 1605, 1490, 1423, 1345, 1314, 1262, 1190, 1112, 1029, 749, 692 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found C, 66.77; H, 5.34; N, 3.49.

(8*R*,9*R*)-8-Acetoxy-8,8a-dihydro-1*H*-oxazolo[3,4-α]pyridine-3,7-dione (73). A solution of **72** (342 mg, 0.865 mmol) in excess formic acid was refluxed for 3.5h. The solution was concentrated *in vacuo*, redissolved in MeOH, and cooled to 0 °C. To this solution 0.432 mL of ammonia (2.0M solution in methanol) was added and stirred for 30 min. The ammonia was then quenched with a few drops of glacial acetic acid, and the solution was concentrated *in vacuo*. Purification by radial PLC and recrystallization from EtOAc afforded 134 mg (73%) of **73** as a white solid, mp 180.8-182.0 °C (dec.); $[\alpha]^{23}_D$ +374.5 (*c* 0.235, MeOH); ^1H (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J* = 7.8 Hz), 5.56 (d, 1H, *J* = 7.7 Hz), 5.42 (d, 1H, *J* = 13.0 Hz), 4.69 (t, 1H, *J* = 8.0 Hz), 4.48 (m, 1H), 4.34 (t, 1H, *J* = 9.2 Hz), 2.23 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 187.4, 169.7, 151.9, 139.2, 107.4, 72.7, 67.9, 55.1, 20.7; IR (thin film, NaCl) 2915, 2849, 1777, 1752, 1677, 1593, 1430, 1372, 1313, 1259, 1192, 1096, 1063

cm^{-1}. Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found C, 51.27; H, 4.50; N, 6.35.

(5*R*,8*R*,9*R*)-8-Acetoxy-5-dodecyl-7-(trifluoromethanesulfonyloxy)-1,5,8,8a-tetrahydro-oxazolo[3,4-α]pyridin-3-one (74). To a solution of iododododecane (0.097 mL, 0.39 mmol) in 5.0 mL of anhydrous diethyl ether cooled to –78 °C was added 0.54 mL of *t*-BuLi (1.45M solution in pentane) dropwise, and the solution stirred for 1h. The lithium reagent was then transferred dropwise through a double-tipped stainless steel needle to a separate flask containing copper(I) bromide-dimethyl sulfide complex (40.2 mg, 0.196 mmol, freshly recrystallized from Me_2S/hexanes) in 2.0 mL of anhydrous THF at –78 °C. This bright yellow solution was stirred for an additional 30 min. Then a solution of **73** (13.8 mg, 0.065 mmol) in 3.0 mL of anhydrous THF was added dropwise, and the solution was stirred for 2 h. Finally, the triflating reagent, 2-[*N,N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine, (160 mg, 0.407 mmol) was added and the reaction flask was stirred at –15 °C overnight (15 h). The reaction mixture was quenched with $NaHCO_3$, extracted with EtOAc, washed with water, and concentrated *in vacuo*. Purification by radial PLC (10-33% EtOAc/hexanes) afforded 20 mg (60%) of **74** as a colorless oil: $[\alpha]^{23}_D$ –41.8 (*c* 0.44, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 6.07 (d, 1H, *J* = 3.8 Hz), 5.43 (d, 1H, *J* = 7.7 Hz), 4.47 (m, 3H), 3.92 (m, 1H), 2.19 (s, 3H), 1.68 (m, 2H), 1.25-1.41 (m, 20H), 0.89 (t, 3H, *J* = 6.6Hz); ^{13}C (75 MHz, $CDCl_3$) δ 170.2, 156.3, 142.2, 123.9, 118.6 (q, J = 318.1 Hz), 67.0, 66.9, 54.0, 50.3, 33.7, 32.1, 29.8, 29.7,

29.6, 29.5, 26.2, 22.9, 20.7, 14.3; IR (thin film, NaCl) 2926, 2855, 1763, 1420, 1216, 1142, 1048 cm^{-1}. HRMS Calcd for $C_{22}H_{35}F_3NO_7S$ 514.2086 $[M + H]^+$, found 514.2104.

(5*R*,8*S*,9*R*)-8-Acetoxy-5-dodecyl-perhydro-oxazolo[3,4-α]pyridin-3-one (75). To a stirred solution of **74** (19.7 mg, 0.038 mmol) in absolute EtOH was added 10% Pt/C (12 mg) and Li_2CO_3 (16 mg, 0.217 mmol). Then the flask was evacuated and back filled with hydrogen under balloon pressure. After 2 h, the reaction was filtered through Celite® with EtOAc, and concentrated *in vacuo*. Purification by flash chromatography (50% EtOAc/hexanes) yielded 12.8 mg (91%) of **75** as a white solid, mp 77.5-78.5 °C; $[\alpha]^{23}_D$ +20.4 (*c* 0.225, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 4.58 (m, 1H), 4.35 (m, 1H), 4.11 (m, 1H), 3.91 (m, 1H), 3.68 (m, 1H), 2.06 (s, 3H), 1.58-1.81 (m, 5H), 1.45 (m, 1H), 1.25 (br s, 20H), 0.88 (m, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 170.3, 157.0, 72.7, 66.4, 53.9, 49.1, 32.1, 30.0, 29.8, 29.8, 29.7, 29.6, 26.5, 24.9, 22.9, 21.2, 14.3; IR (thin film, NaCl) 2922, 2850, 1738, 1425, 1245, 1049 cm^{-1}. HRMS Calcd for $C_{22}H_{38}NO_4$ 368.2801 $[M + H]^+$, found 368.2799.

(2*S*)-1-[(1*R*,2*S*)-*trans*-2-(α-Cumyl)cyclohexyloxycarbonyl]-2-(hydroxymethyl)-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (80). To a stirred solution of **50** (52 mg, 0.084 mmol) in 5 mL of EtOH was added 50 mg of 20% $Pd(OH)_2/C$ and 1 mL of cyclohexene. The solution was heated to reflux and stirred for 6 h. The reaction mixture was then cooled to rt, filtered through Celite® with EtOAc, and concentrated

in vacuo. Purification by radial PLC (20% EtOAc/hexanes) and recrystallization from methanol gave 41 mg (93%) of **80** as a white solid, mp 129.5-130.8 °C; $[\alpha]^{23}_{D}$ -54.5 (*c* 0.84, $CHCl_3$); ^1H (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.10-7.34 (m, 5H), 4.86 (m, 1H), 3.31 (m, 1H), 2.79 (m, 1H), 1.68-2.40 (m, 9H), 1.18-1.37 (m, 9H), 0.99-1.05 (m, 22H); ^{13}C (75 MHz, $CDCl_3$) δ 196.6, 152.4, 147.9, 137.6, 128.3, 125.4, 110.4, 78.5, 62.0, 52.8, 51.2, 39.7, 37.9, 33.7, 31.3, 27.0, 26.1, 24.9, 21.5, 19.1, 11.3; IR (thin film, NaCl) 3424, 2941, 2864, 1721, 1653, 1571, 1465, 1382, 1324, 1300, 1257, 1010 cm^{-1}. Anal. Calcd for $C_{31}H_{49}NO_4Si$: C, 70.54; H, 9.36; N, 2.65. Found C, 70.53; H, 9.48; N, 2.56.

(2*S*)-1-Benzyloxycarbonyl-2-benzyloxymethyl-2,3-dihydro-4-pyridone (83). To a solution of **65** (85 mg, 0.391 mmol) in 20 mL of THF, cooled to -78 °C, was added 0.246 mL *n*-butyllithium (1.75 M in hexanes), and the mixture was stirred for 20 min. Benzyl chloroformate (0.067 mL, 0.470 mmol) was added, and the solution was stirred at -78 °C for 30 min. The reaction was quenched with saturated $NaHCO_3$ and warmed to rt. The solution was extracted with EtOAc, washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by radial PLC (40% EtOAc/hexanes) afforded 117 mg (85%) as a colorless oil: ^1H (300 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* = 7.6 Hz), 7.31 (m, 10H), 5.30 (d, 1H, *J* = 8.3 Hz), 5.24 (s, 2H), 4.83 (d, 1H, *J* = 6.2Hz), 4.47 (dd, 2H, *J* = 12.0, 8.2 Hz), 3.57 (m, 2H), 2.84 (dd, 1H, *J* = 16.9, 7.0 Hz), 2.66 (d, 1H, *J* = 16.8 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 192.4, 152.7, 141.9, 137.7, 135.1, 128.8, 128.5, 127.9, 127.6, 107.3, 73.4, 69.2, 68.4,

52.5, 37.5; IR (thin film, NaCl) 3031, 2861, 1730, 1672, 1605, 1423, 1385, 1327, 1270, 1218, 1195, 1112 cm^{-1}.

(2*R*,3*R*)-3-Acetoxy-1-benzyloxycarbonyl-2-benzyloxymethyl-2,3-dihydro-4-pyridone (84). To a flask containing **83** (32 mg, 0.091 mmol) under a dry nitrogen atmosphere was added $Pb(OAc)_4$ (104 mg, 0.235 mmol, freshly recrystallized from glacial acetic acid and dried *in vacuo*). The flask was sealed under nitrogen, and the reaction mixture was dissolved in 15 mL of toluene, heated to reflux and stirred for 18h. By TLC, the reaction was not complete, yet no active $Pb(OAc)_4$ seemed to be present, so additional $Pb(OAc)_4$ (50 mg, 0.11 mmol) was added and refluxing was resumed for another 6 h. After cooling to rt, the solution was filtered through silica gel with EtOAc and then concentrated *in vacuo*. Purification by radial PLC (20% EtOAc/hexanes) gave 16 mg (43%) of **84** as a colorless oil: ^1H (300 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 8.4 Hz), 7.20-7.37 (m, 10H), 5.85 (d, 1H, J = 8.6 Hz), 5.25 (m, 3H), 4.78 (m, 1H), 4.46 (s, 2H), 3.65 (m, 2H), 2.08 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 186.7, 169.6, 152.6, 143.0, 137.4, 134.9, 129.0, 128.6, 128.0, 127.7, 105.7, 73.6, 70.2, 69.6, 67.5, 57.6, 21.1; IR (thin film, NaCl) 3028, 2868, 1745, 1729, 1625, 1600, 1387, 1317, 1264, 1205, 1114, 1029 cm^{-1}.

(2*S*)-1-[(1*R*,2*S*)-*trans*-2-(α-Cumyl)cyclohexyloxycarbonyl]-2-(benzyloxymethyl)-2,3-dihydro-4-pyridone (90). To a solution of **50** (100 mg, 0.162 mmol) in 5 mL of chloroform was added 5 mL of trifluoroacetic acid, and the

solution was heated to reflux for 3h. After concentration *in vacuo*, purification by radial PLC (5-10% EtOAc/hexanes) produced 73 mg (98%) of **90** as a colorless oil: $[\alpha]^{23}_D$ –8.9 (*c* 1.99, $CHCl_3$); ^1H (300 MHz, $(CD_3)_2SO$, 100 °C) δ 7.20-7.37 (m, 9H), 7.10 (t, 2H, *J* = 7.0 Hz), 4.98 (d, 1H, *J* = 7.8 Hz), 4.73 (m, 1H), 4.43 (m, 2H), 3.38 (br s, 1H), 3.33 (m, 2H), 2.58 (dd, 1H, *J* = 16.8 & 7.5 Hz), 2.17-2.28 (m, 2H), 1.86 (d, 1H, *J* = 11.7 Hz), 1.61-1.76 (m, 3H), 1.15-1.26 (m, 10H); ^{13}C (75 MHz, $(CD_3)_2SO$, 100 °C) δ 190.6, 151.3, 150.5, 141.2, 137.5, 127.6, 127.4, 126.9, 126.7, 124.4, 105.3, 78.6, 77.1, 71.9, 67.6, 50.7, 49.7, 36.5, 32.0, 28.8, 25.8, 24.7, 23.5, 22.1; IR (thin film, NaCl) 2959, 2932, 2860, 1716, 1673, 1606, 1496, 1451, 1422, 1367, 1328, 1271, 1220, 1193, 1114, 1076, 1018, 968, 953, 765, 700 cm^{-1}. Anal. Calcd for $C_{29}H_{35}NO_4$: C, 75.46; H, 7.64; N, 3.03. Found C, 75.55; H, 7.71; N, 3.01.

(2*R*, 3*R*)-3-Acetoxy-1-[(1*R*,2*S*)-*trans*-2-(α-cumyl)cyclohexyloxycarbonyl]-2-(benzyloxymethyl)- 2,3-dihydro-4-pyridone (92). To a flask containing **90** (33 mg, 0.072 mmol) under a dry nitrogen atmosphere was added $Pb(OAc)_4$ (82 mg, 0.19 mmol, freshly recrystallized from glacial acetic acid and dried *in vacuo*). The flask was sealed under nitrogen, and the reaction mixture was dissolved in 15 mL of toluene, heated to reflux and stirred for 18 h. By TLC, the reaction was not complete, yet no active $Pb(OAc)_4$ seemed to be present, so additional $Pb(OAc)_4$ (32 mg, 0.072 mmol) was added and refluxing was resumed for another 6 h. After cooling to rt, the solution was filtered through silica gel with EtOAc and then concentrated *in vacuo*. Purification by radial PLC (20% EtOAc/hexanes) gave 23

mg (62%) of **92** as a colorless oil: ^{1}H (300 MHz, $(CD_3)_2SO$, 100 °C) δ ; ^{13}C (75 MHz, $(CD_3)_2SO$, 100 °C) δ 186.6, 169.4, 152.7, 143.5, 137.4, 128.6, 128.5, 128.2, 128.0, 127.8, 125.4, 125.1, 125.0, 124.9, 104.1, 79.0, 73.5, 69.8, 66.9, 56.8, 51.0, 39.4, 33.4, 31.0, 26.7, 25.9, 24.8, 21.0; IR (thin film, NaCl) 2924, 2856, 1747, 1717, 1675, 1602, 1449, 1419, 1368, 1321, 1262, 1207, 1117, 1024, 951, 764, 700 cm^{-1}. Anal. Calcd for $C_{31}H_{37}NO_6$: C, 71.65; H, 7.18; N, 2.70. Found C, 71.47; H, 7.19; N, 2.85.

References

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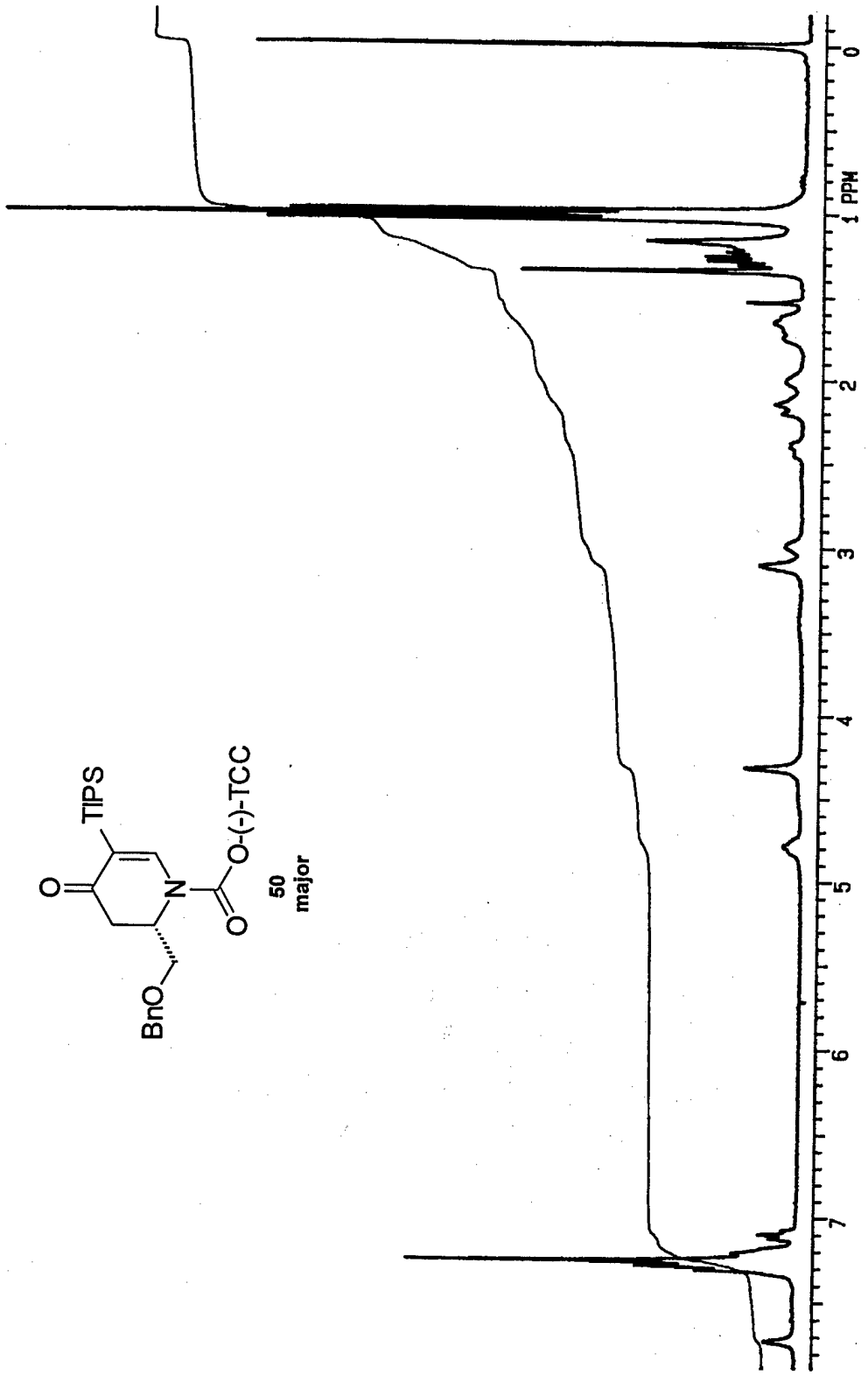
Appendix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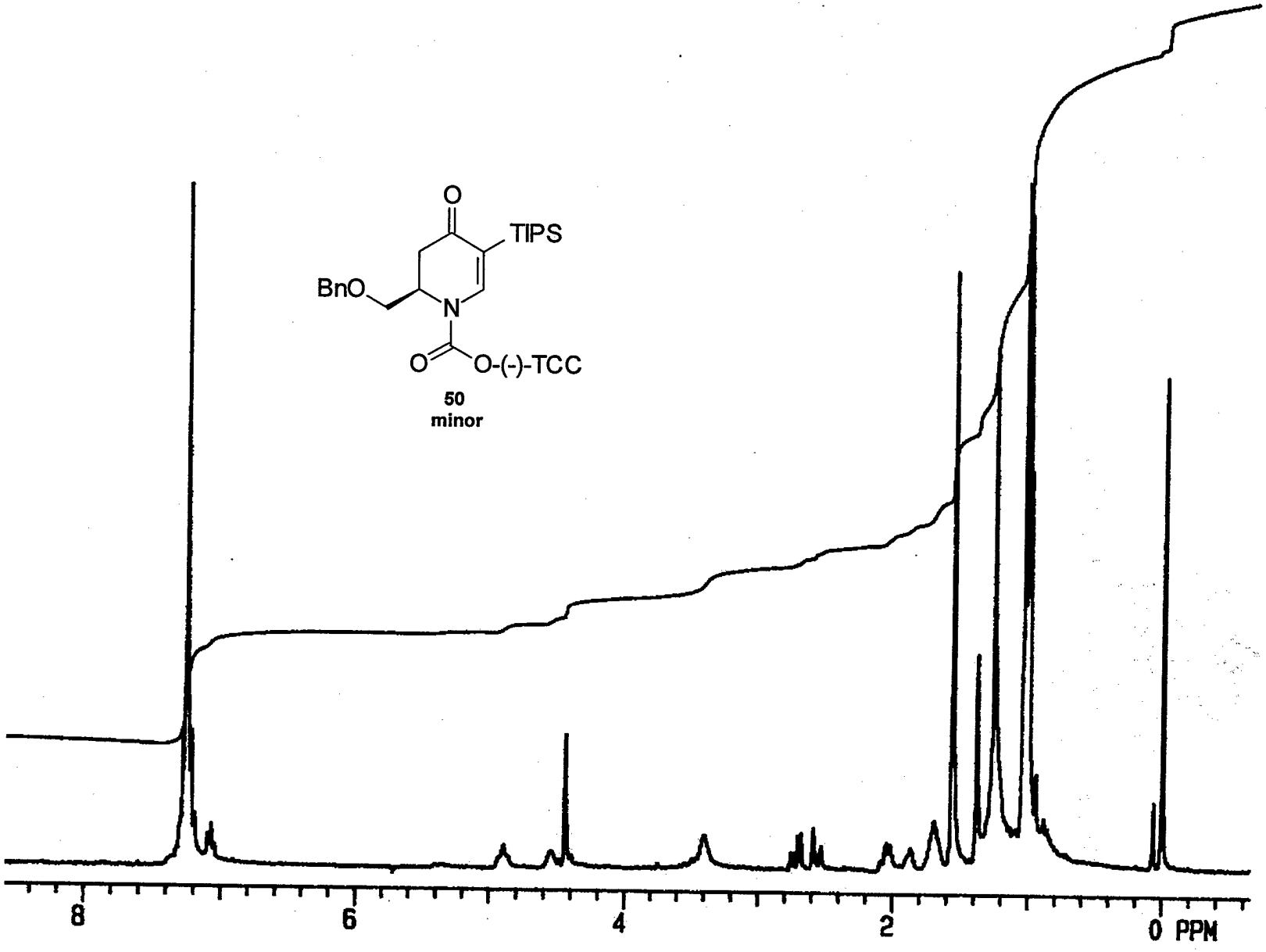
O-(-)-TCC
BnO
50
major
0
1 PPM
2
3
4
5
6
7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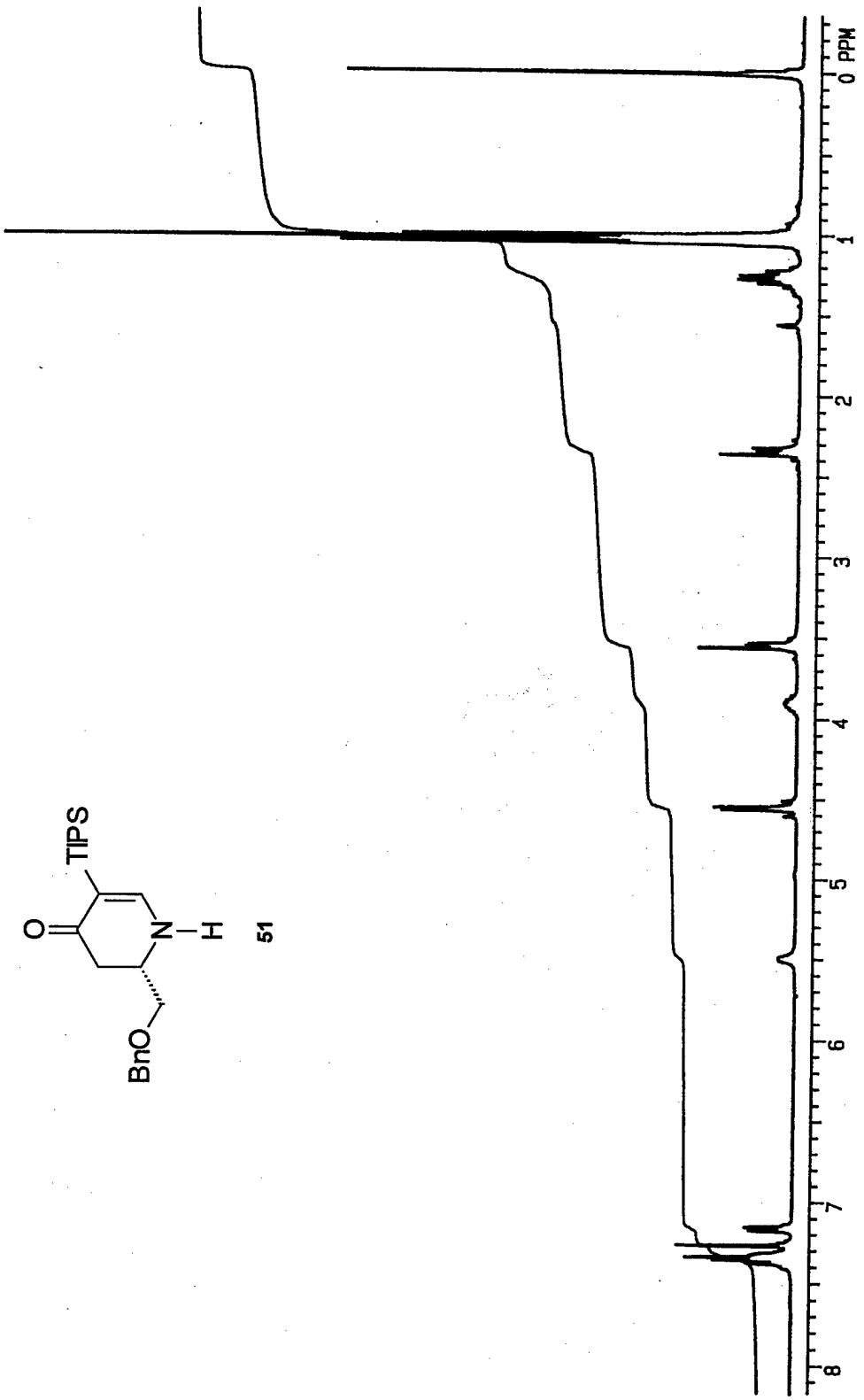
BnO
N
O
O-(-)-TCC
50
minor
8
6
4
2
0 PPM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N
H
BnO
51
0 PPM
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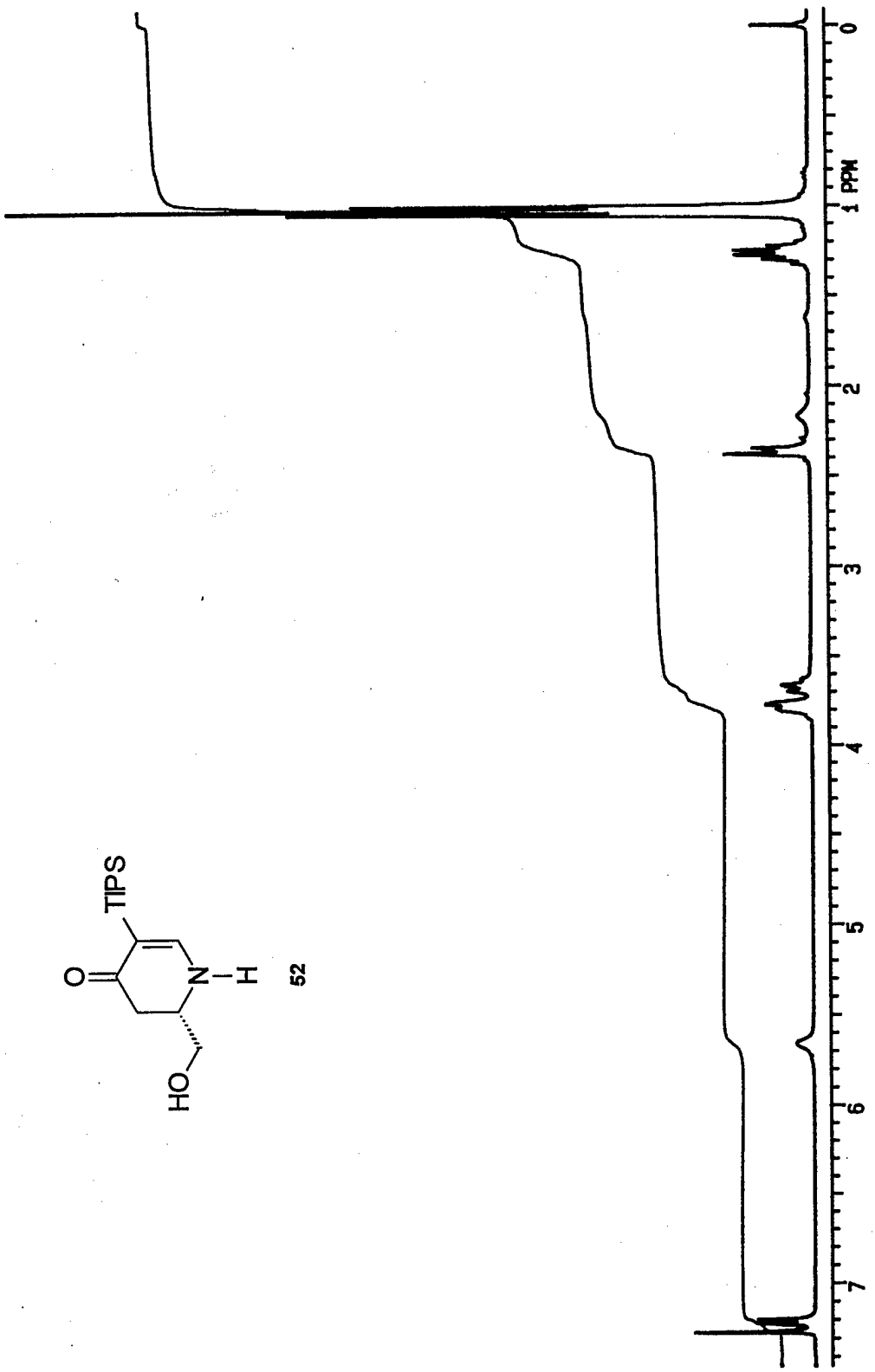
2
3
4
5
6
7
8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HO
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1 PPM
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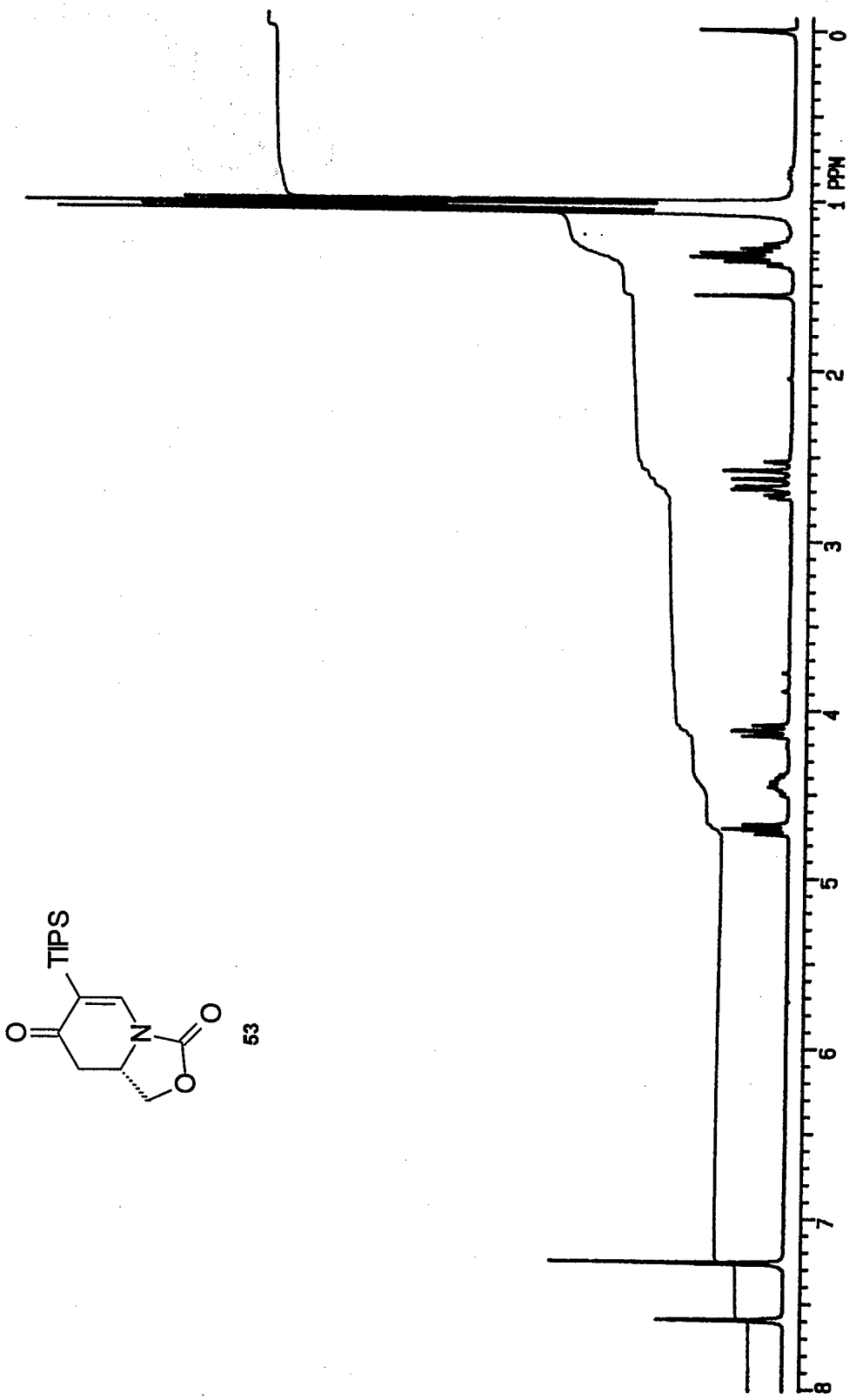
4
5
6
7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O
O
53
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3
4
5
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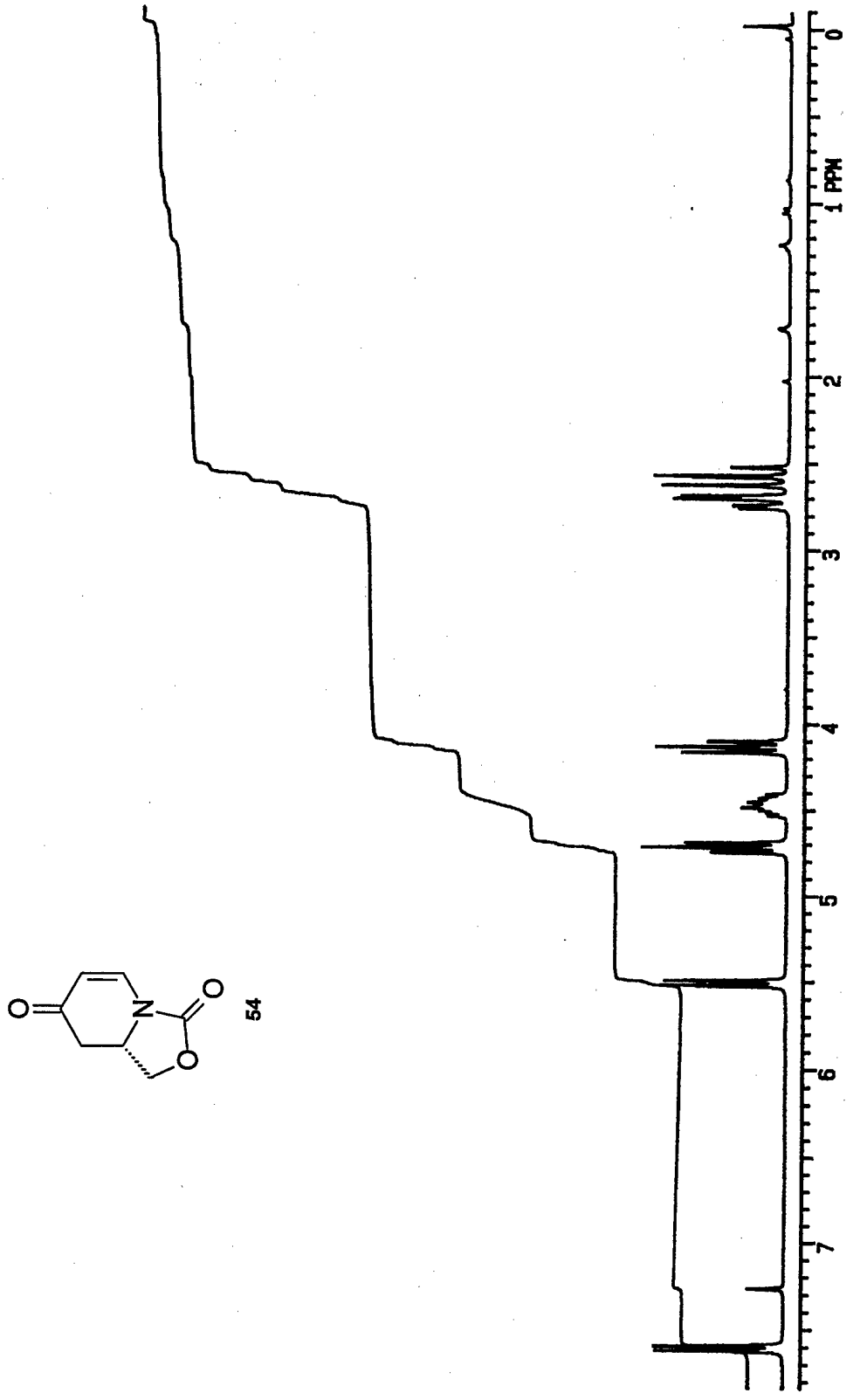
7
8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N
O
54
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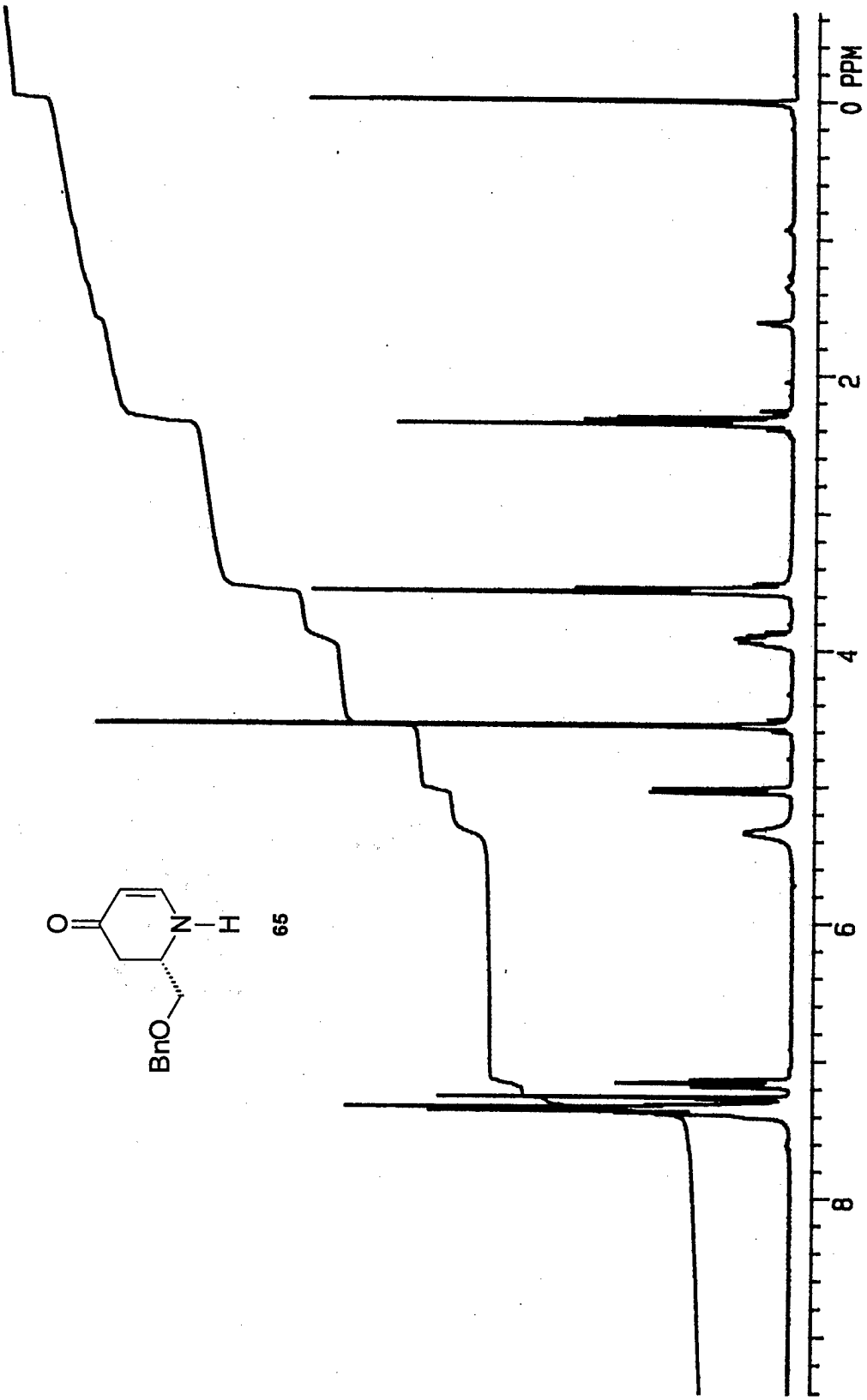
2
3
4
5
6
7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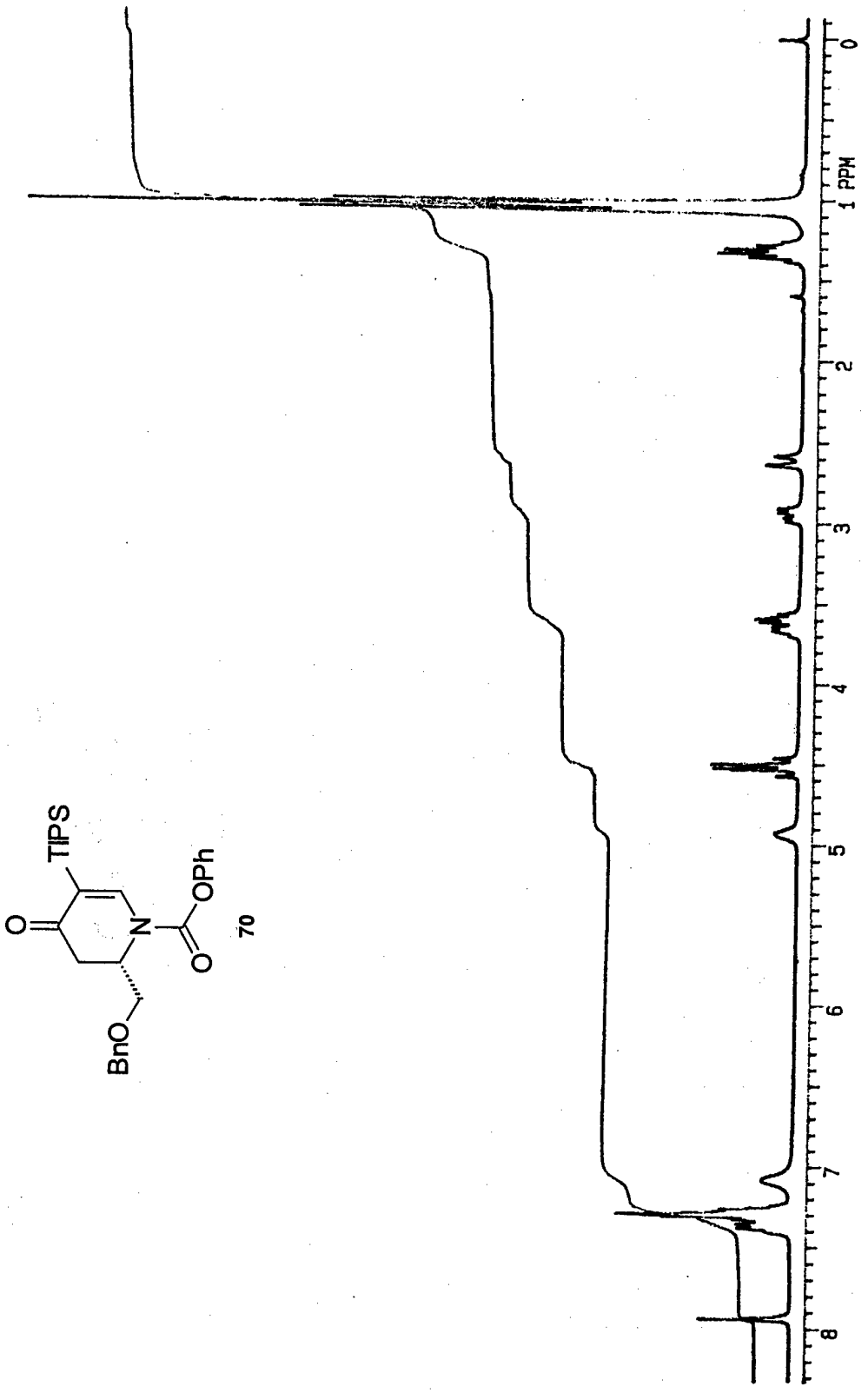
N—H
BnO
65
8
6
4
2
0 PPM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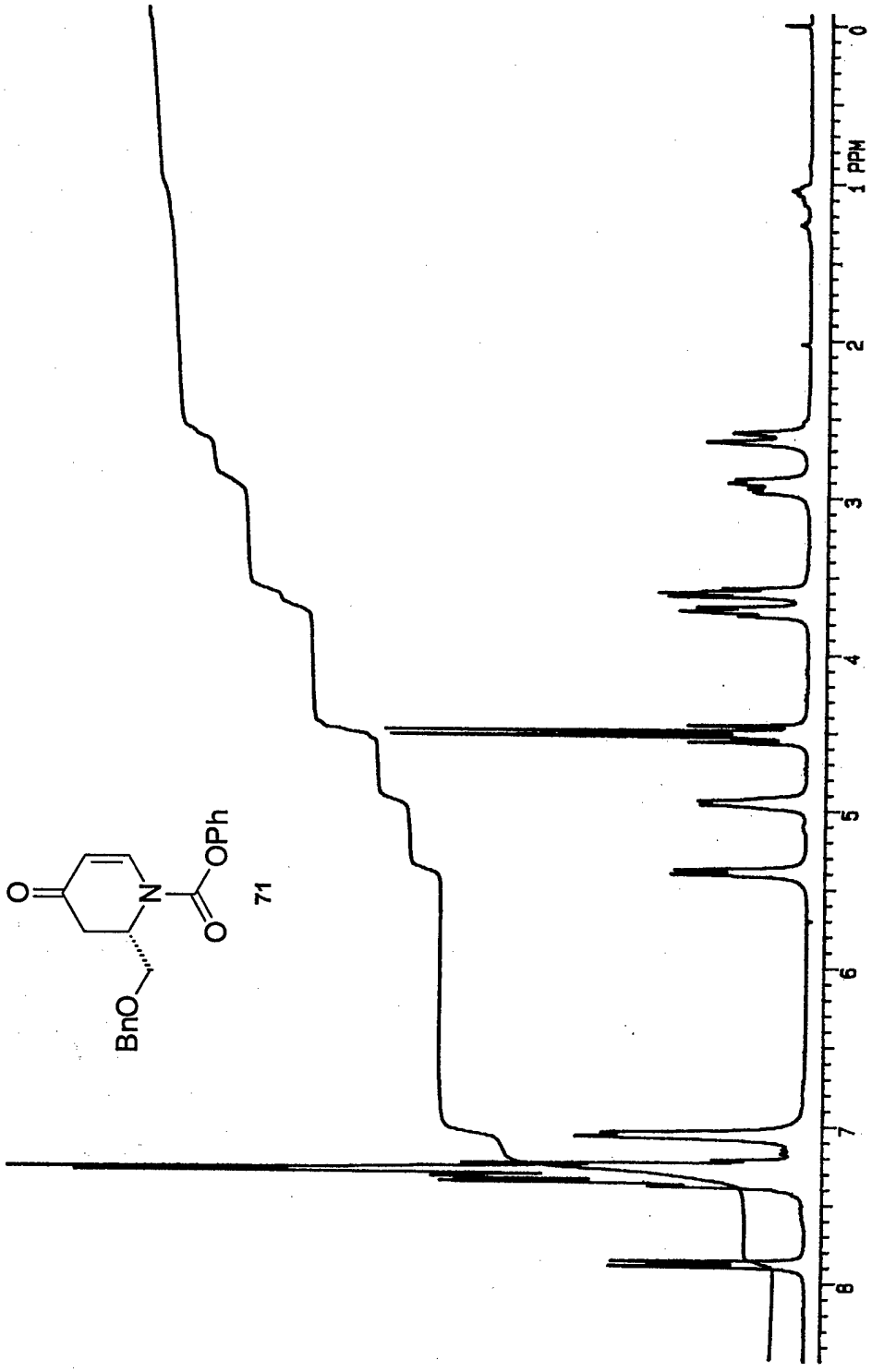
6
7
8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BnO
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7
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3
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1 PPM
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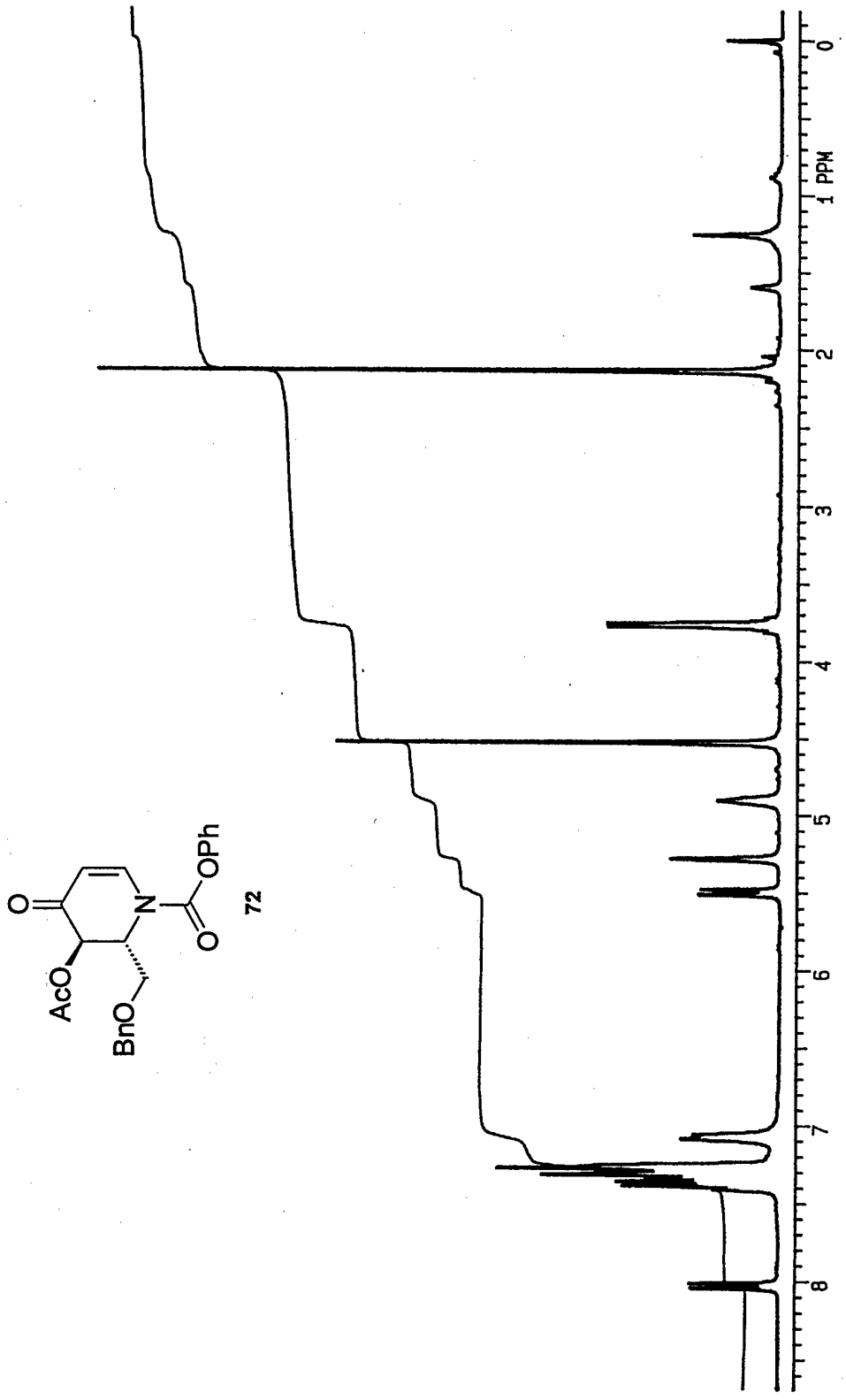
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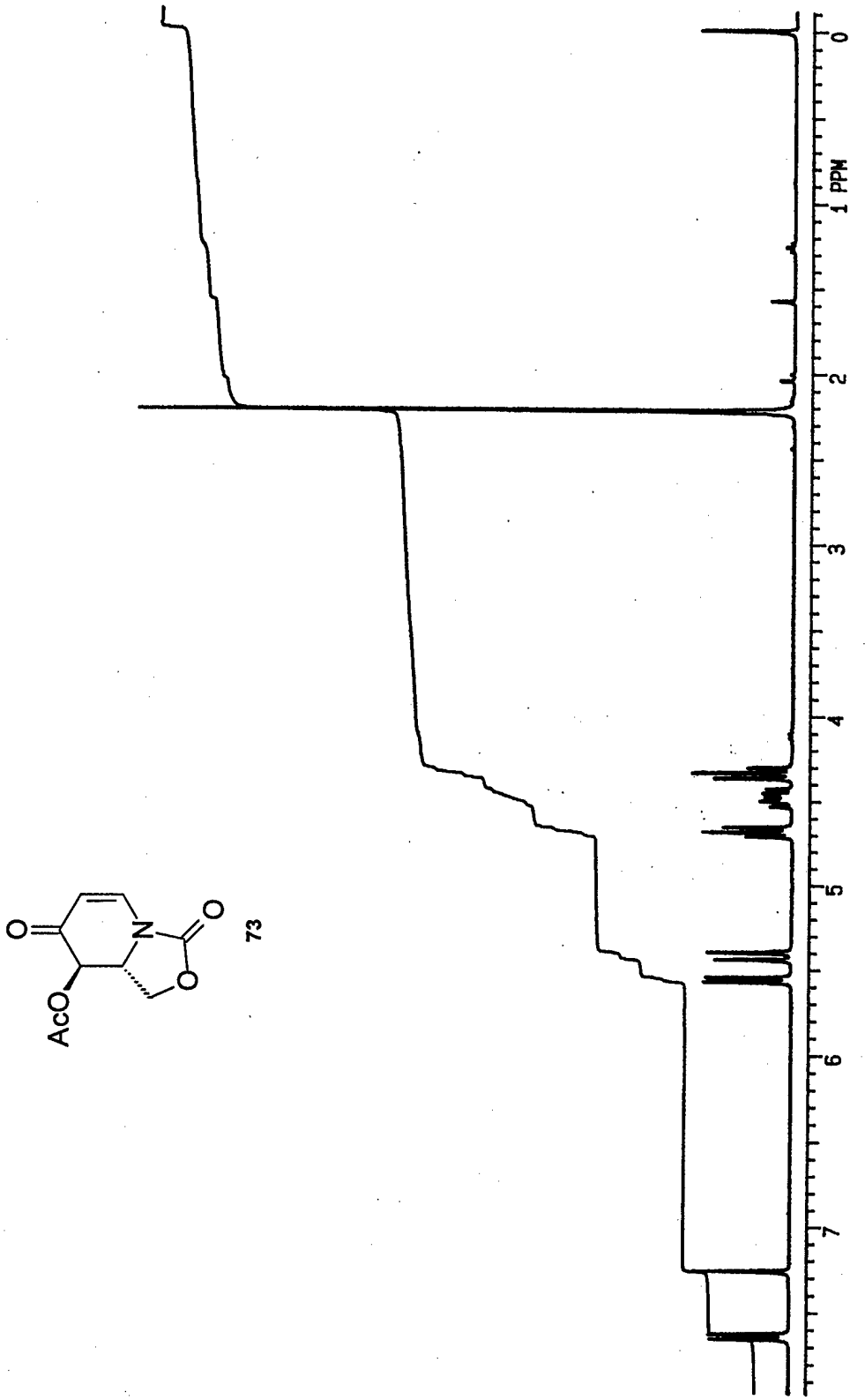
BnO
N
O
OPh
72
8
7
6
5
4
3
2
1 PPM
0



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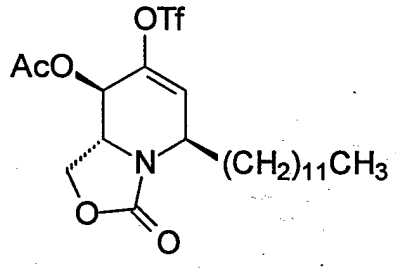

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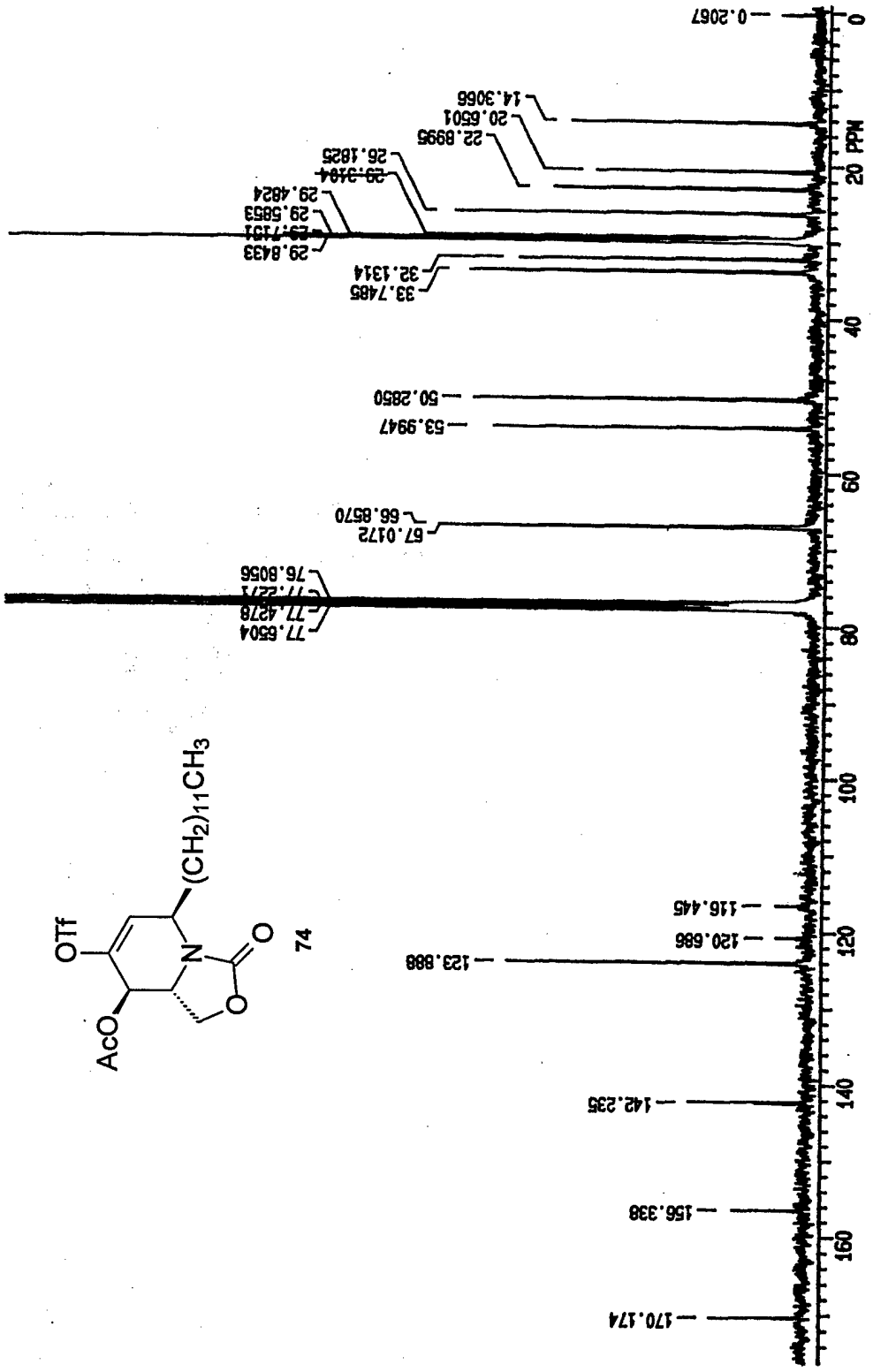
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29.5853
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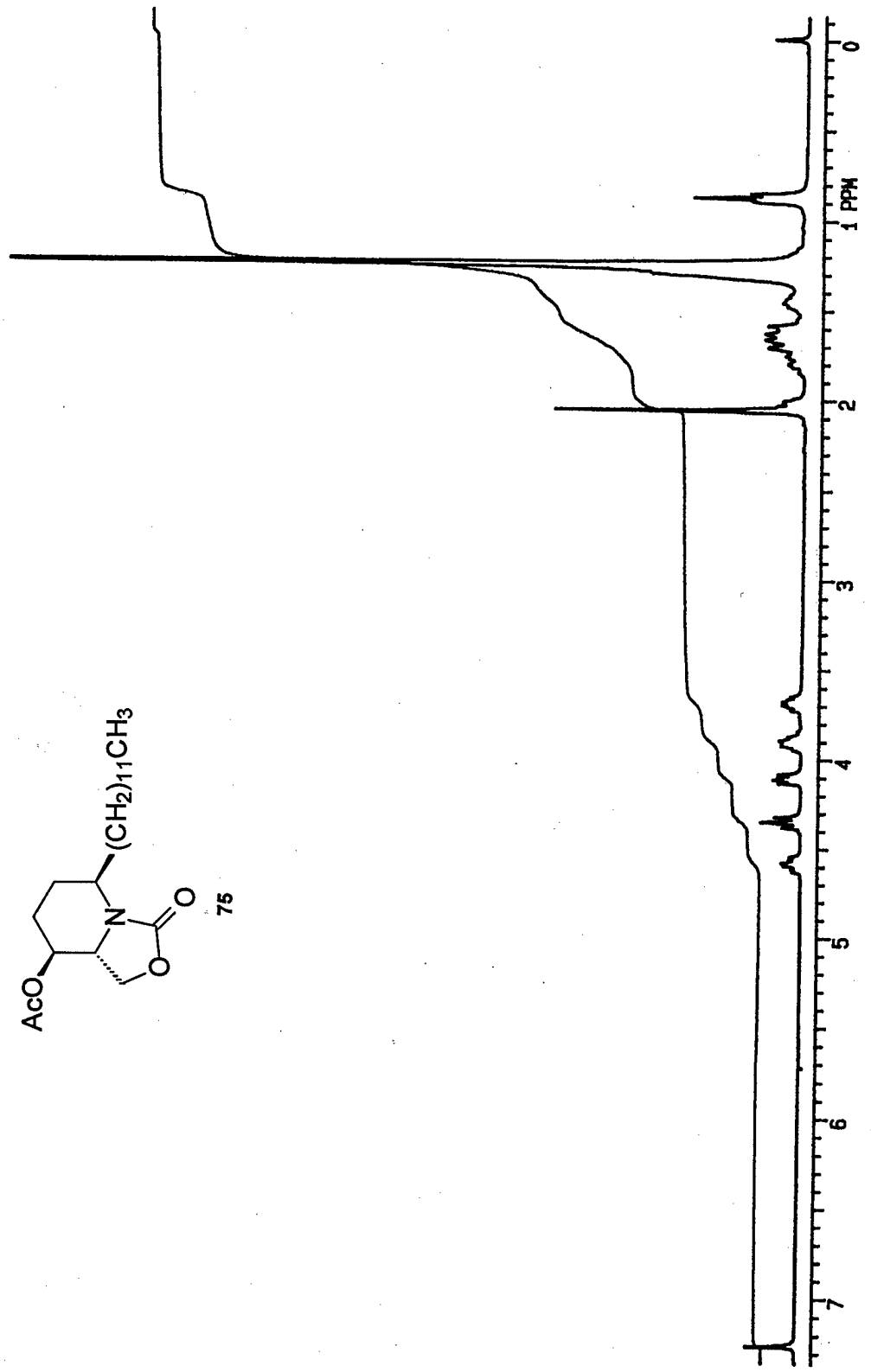
29.8433
32.1314
33.7485
50.2850
53.9947
66.8570
67.0172
76.8056
77.2271
77.4278
77.6504
116.445
120.686
123.888
142.235
156.338
170.174
0
20
40
60
80
100
120
140
160
PPM
OTf
AcO
O
N
O
$(CH_2)_{11}CH_3$
74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O
O
75
0
1 PPM
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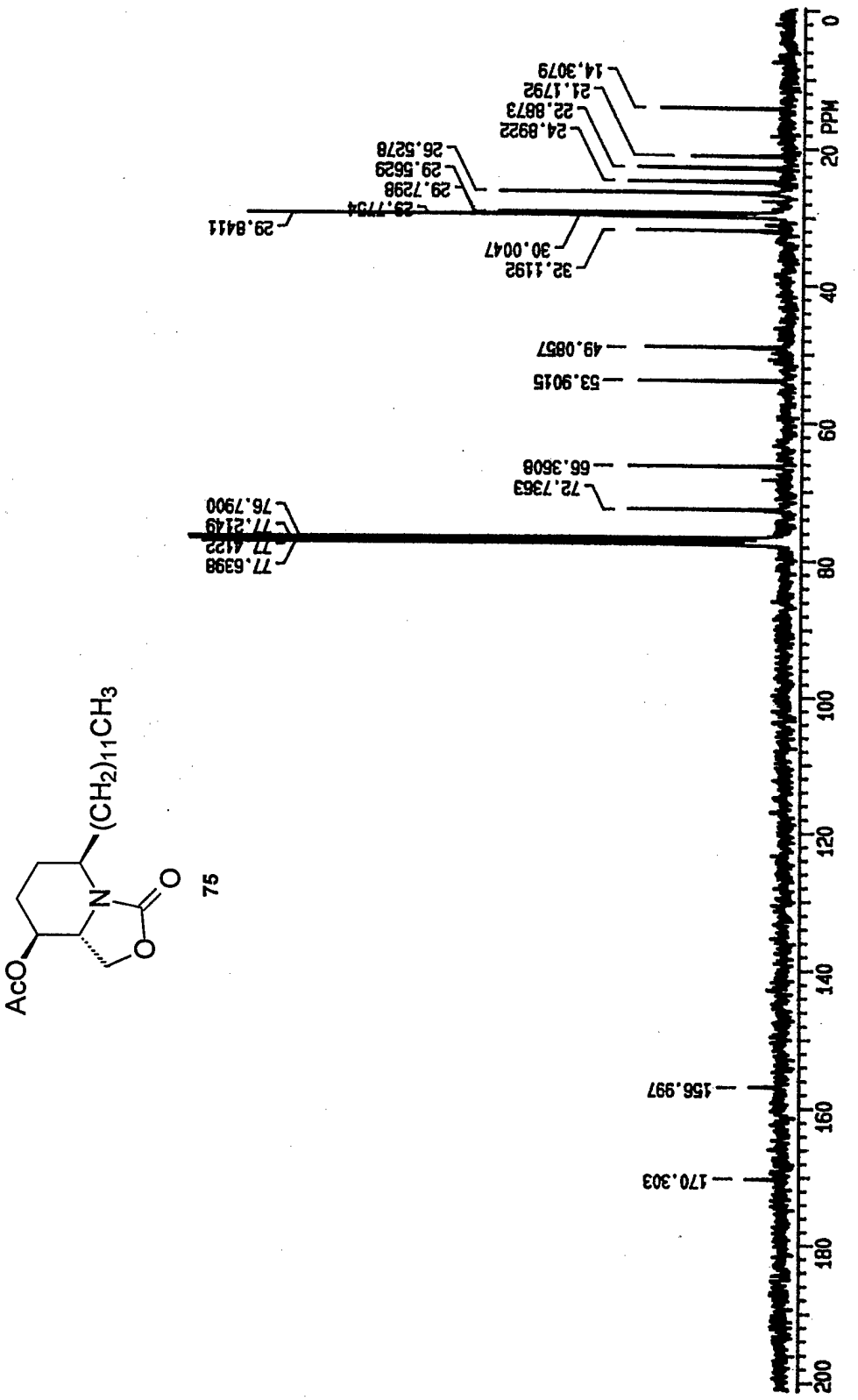
3
4
5
6
7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77.6398
156.997
170.303
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100
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(CH2)11CH3
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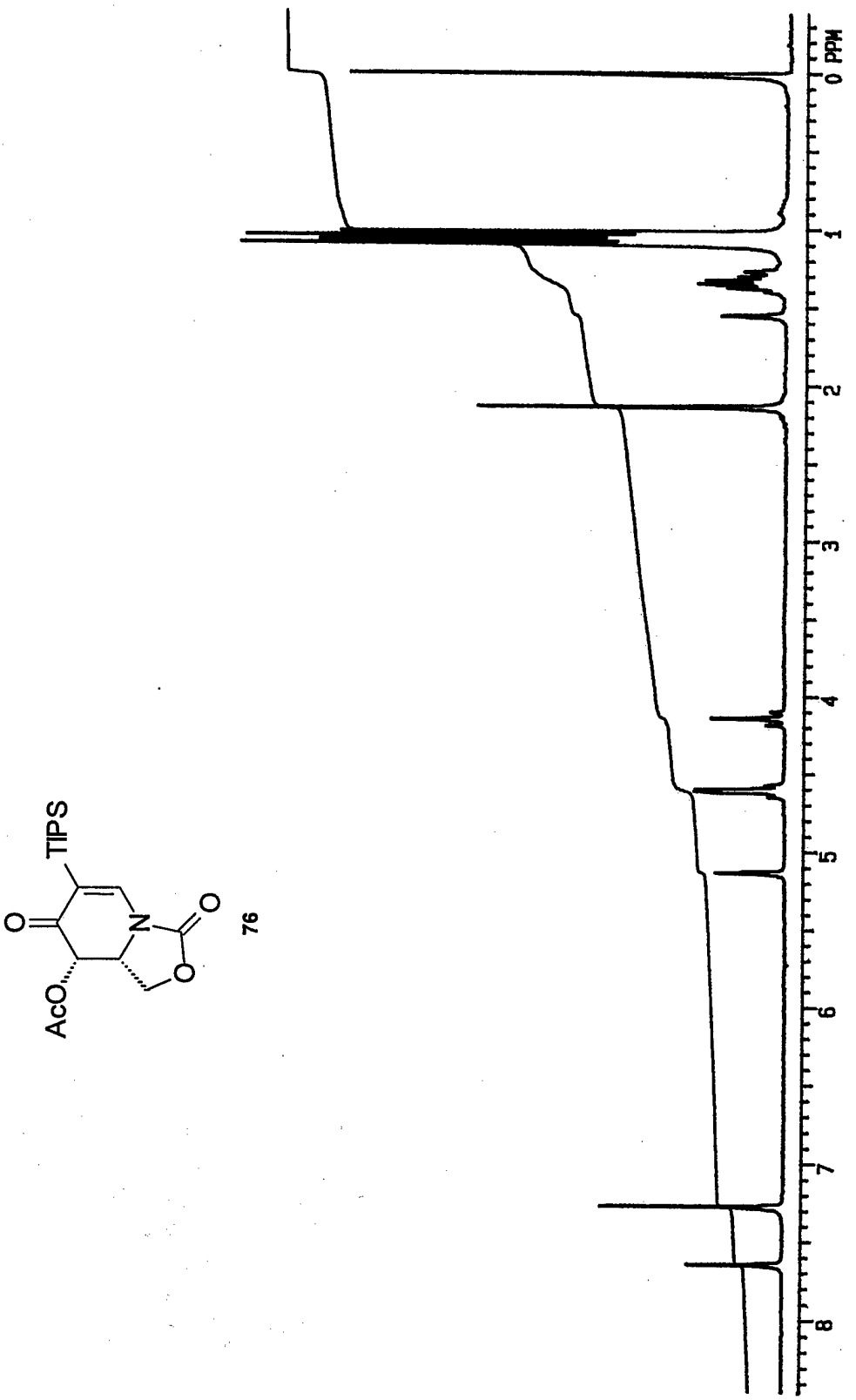
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2
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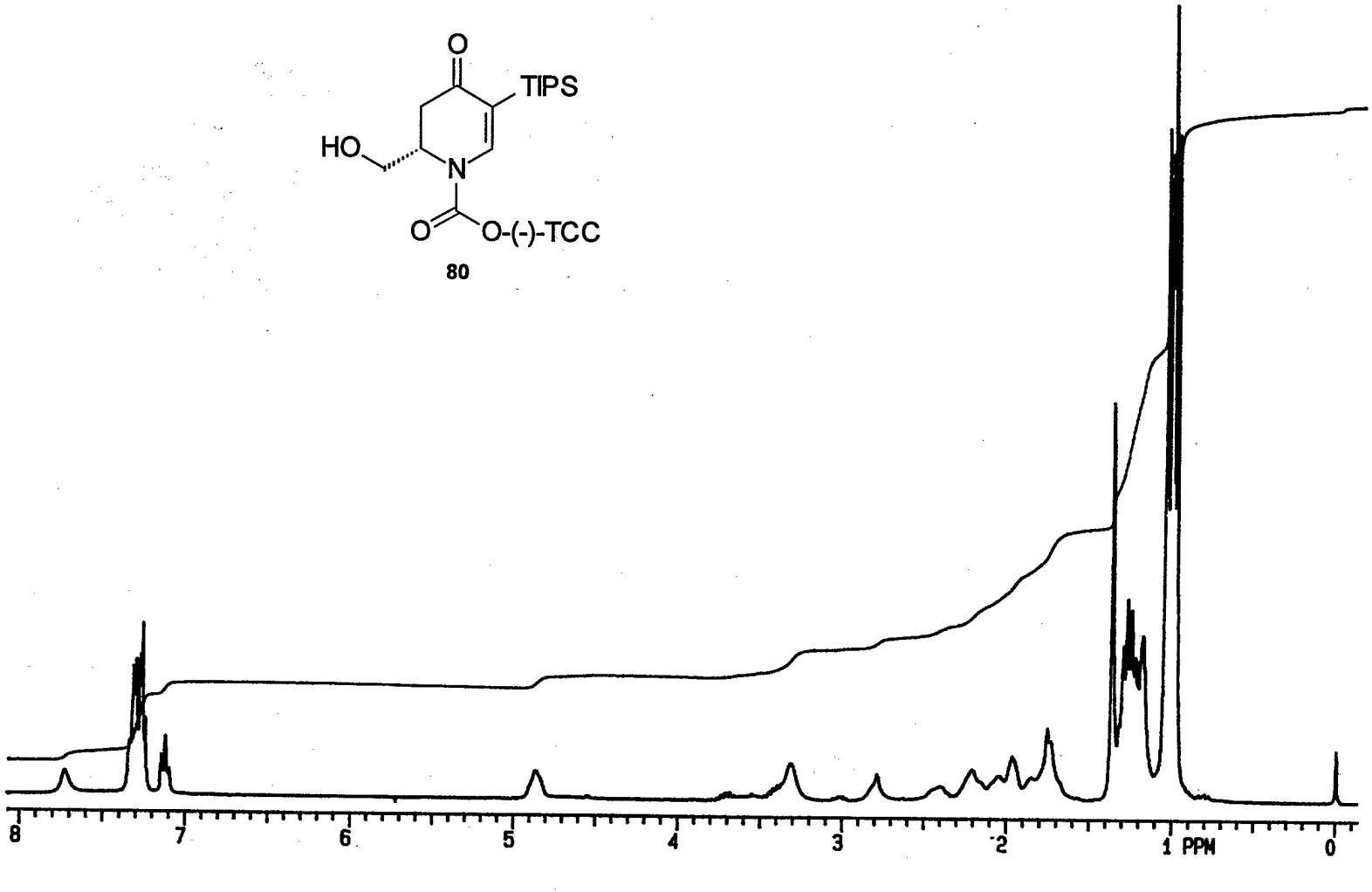
4
5
6
7
8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2
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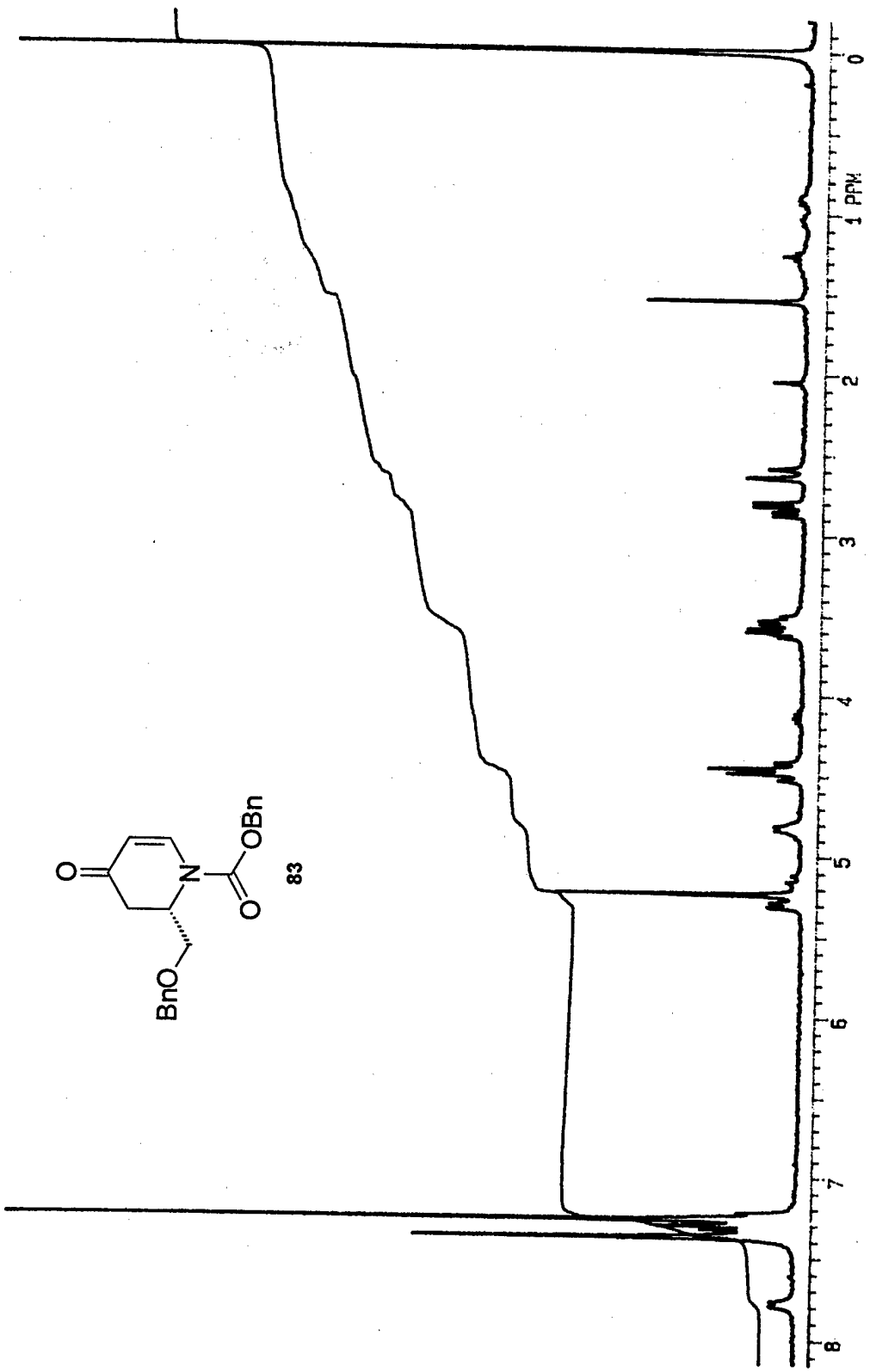
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6
7
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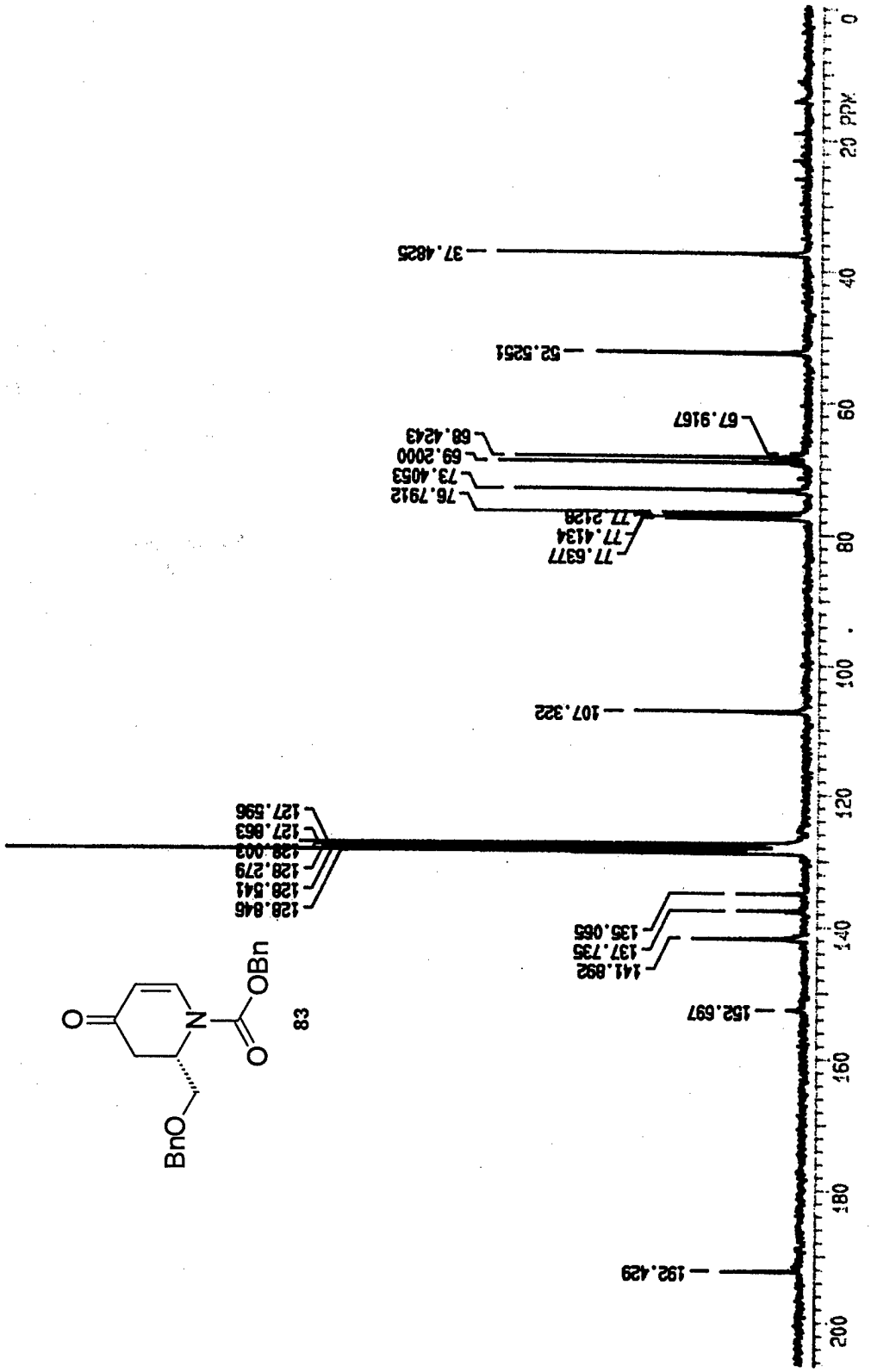
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128.279
128.541
128.846
135.065
137.735
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152.697
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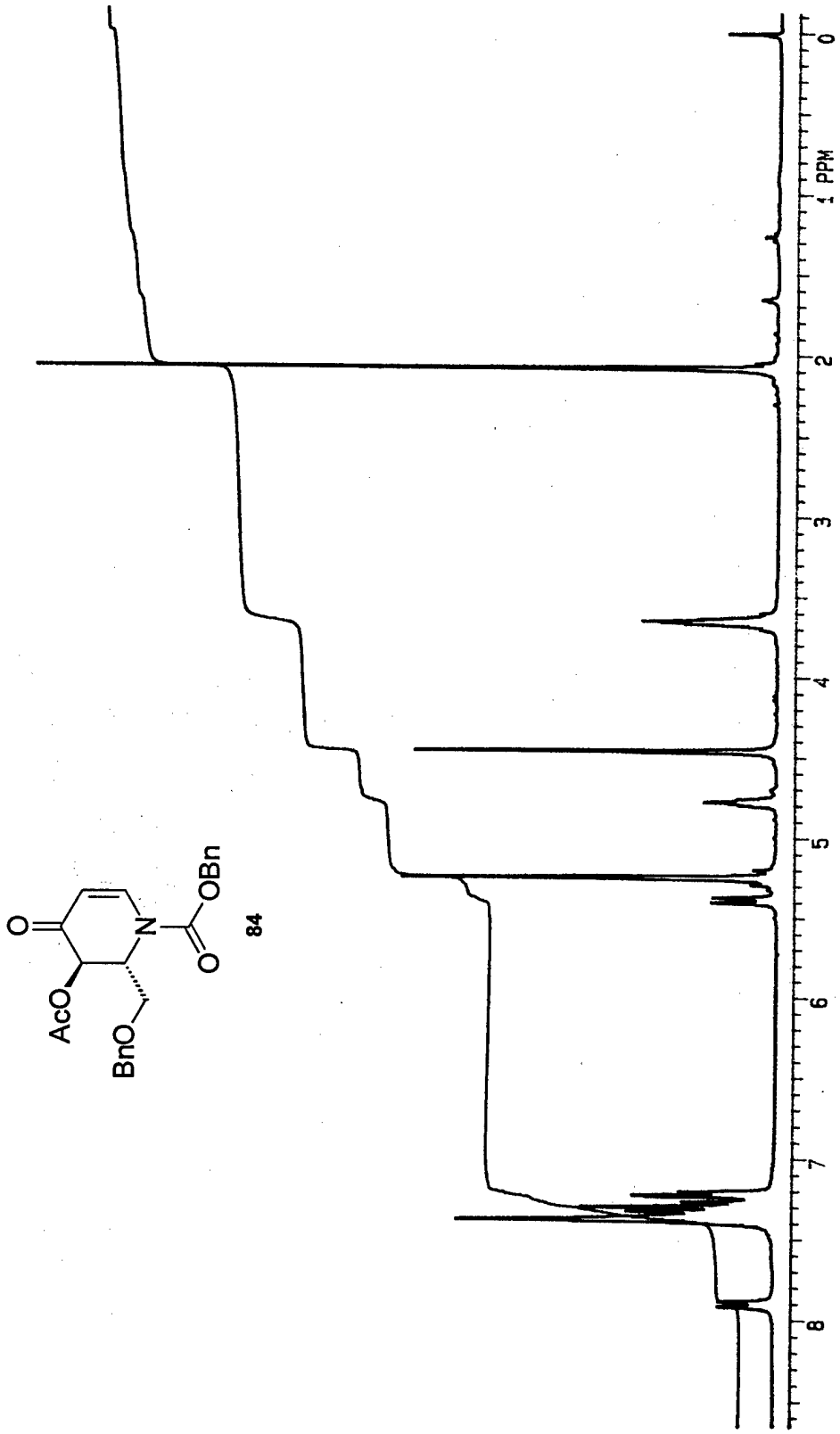
O
BnO
83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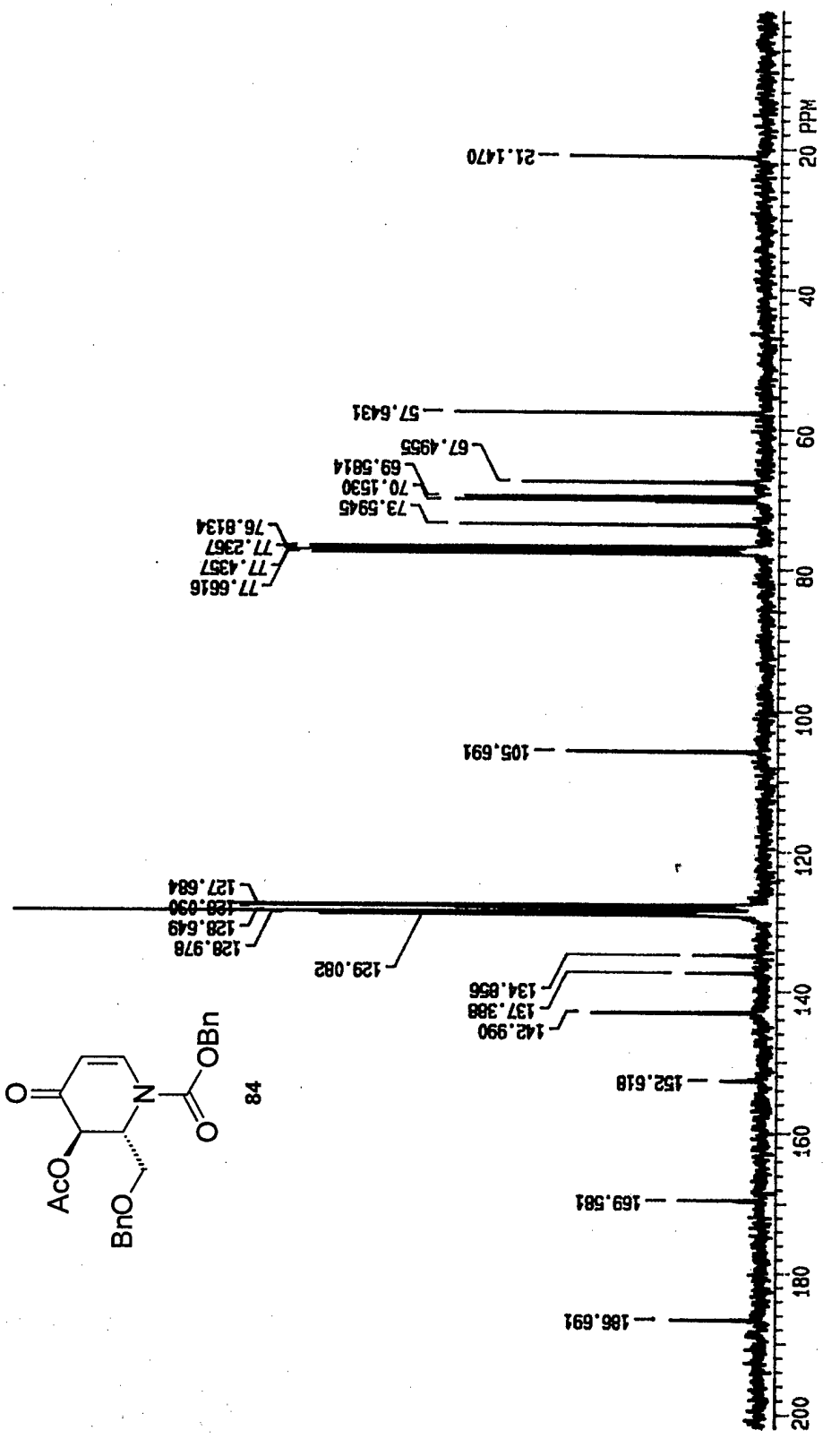
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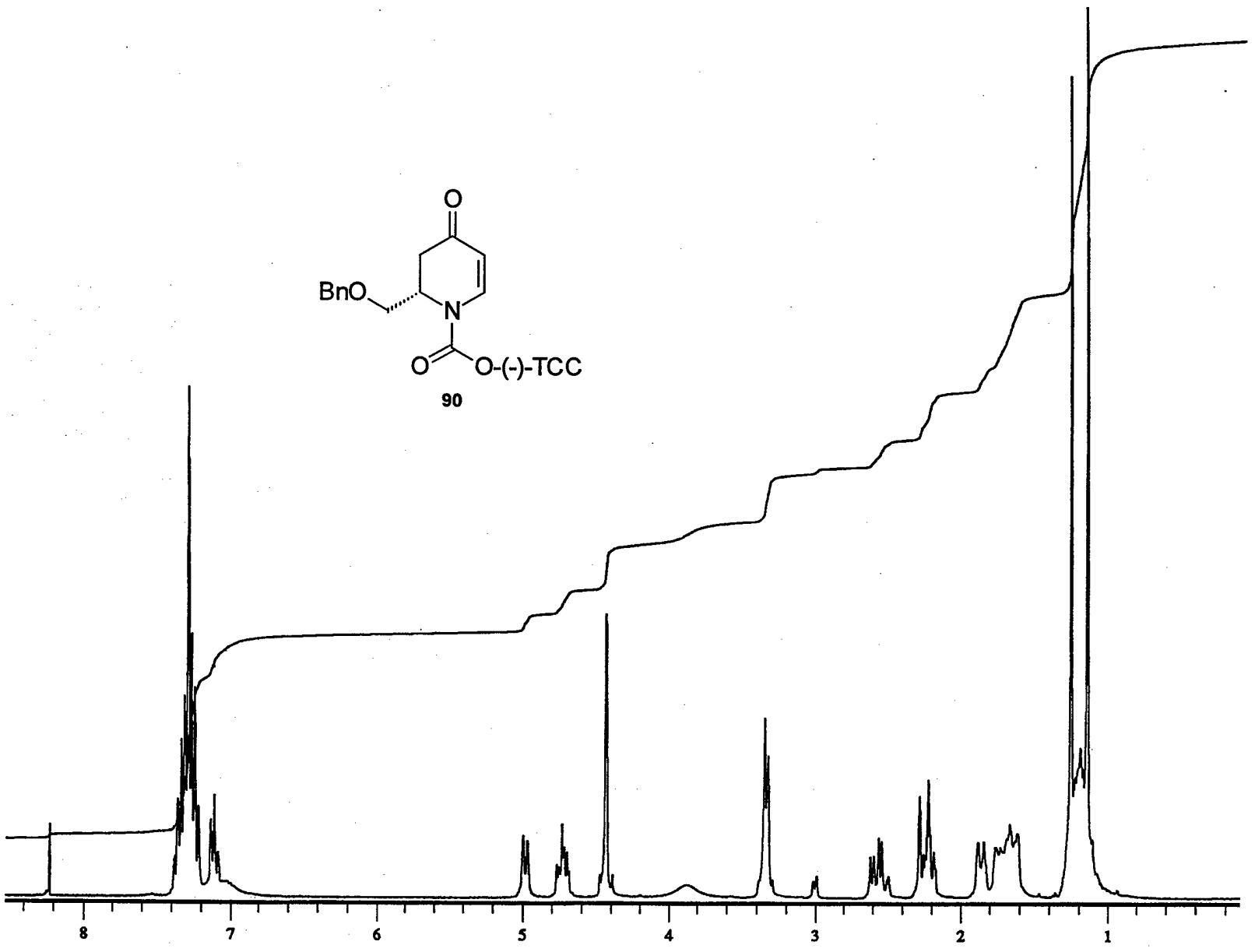
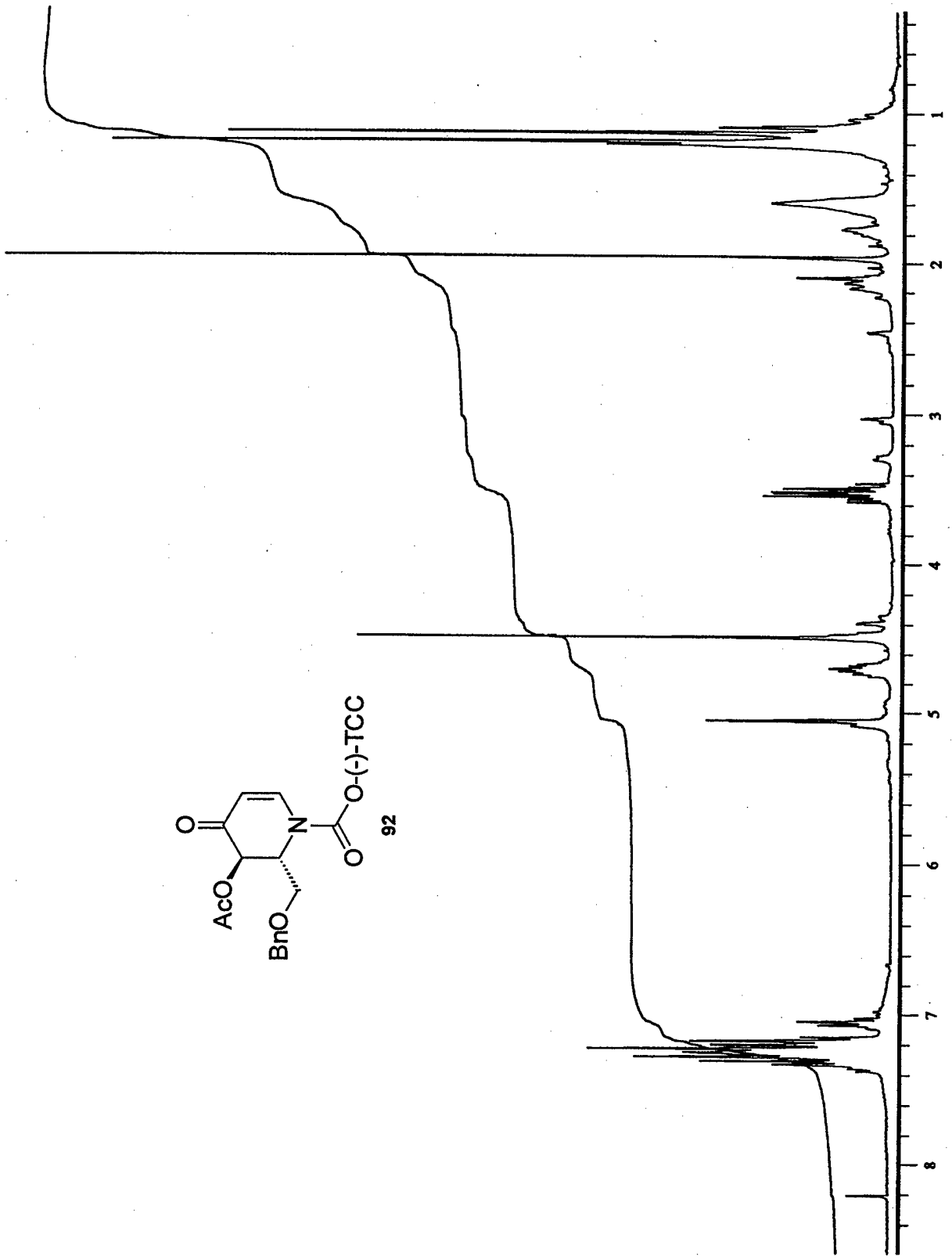
BnO
84



90


O
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O
O-(-)-TCC
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BnO
92
1
2
3
4
5
6
7
8